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USE OF D4 AND 5-HT2A ANTAGONISTS, INVERSE AGONISTS OR PARTIAL
AGONISTSField of the invention

The invention relates to the field of neuropsychiatry. More specifically, the invention
5 relates to the use of compounds, which have D4 and 5-HT2A antagonist, inverse agonist or partial agonist activity, for the preparation of medicaments.

Background of the invention

Conventionally, mental disorders are divided into types based on criteria sets with defining features. DSM-IV (*American Psychiatric Association*, (1993 – ISBN 0 – 89042 – 061 – 0))
10 is the in the art well-known golden standard of such a categorical classification. In DSM-IV, there is no assumption that each category of mental disorder is a completely discrete entity with absolute boundaries dividing it from other mental disorders or from no mental disorder. There is also no assumption that all individuals described as having the same mental disorder are alike in all important ways. Individuals sharing a diagnosis are likely to
15 be heterogeneous even in regard to the defining features of the diagnosis. Thus, the categorical defined mental disorders as mood and anxiety disorders are having an external and even internal variable co-incidence of symptoms concerning e.g. mood, anxiety, perception, feeding, somatic sensations, sexual functions, sleep, cognitive functioning, impulse control, attention, substance use, personality, bereavement, identity, phase of life, abuse or neglect and other aspects of behavior.

In a dimensional system; clinical presentations are classified based on quantification of attributes i.e. dysfunctions rather than the assignment to categories and works best in describing phenomena that are distributed continuously and that do not have clear boundaries.
25 Emotion dysregulation is known as such an attribution or dysfunction that plays an important role in the development and course of mental disorders (*Gross, J. J. & Munoz, R. F., 1995, Emotion regulation and mental health, Clinical Psychology: Science and Practice, 2, 151-164; Mennin, D.S., Heimberg, R. G., Turk, C. L. & Fresco, D. M., 2002, Applying an emotion regulation framework to integrative approaches to generalized anxiety disorder, Clinical Psychology: Science and Practice, 9, 85-90; Linehan, M. M., 1993, Cognitive-behavioral treatment of borderline personality disorder, New York, The Guilford Press; Gratz, K. L., Roemer, L., 2001 & 2004, Multidimensional assessment of emotion regulation and dysregulation: development, factor structure, and initial validation*)

of the Difficulties in Emotion Regulation Scale, Annual meeting of the Association for Advancement of Behavior Therapy, Nov. 2001 & Journal of Psychopathology and Behavioral Assessment, Vol. 26, No. 1, March 2004) besides behavioural and cognitive dysfunctions. D4 dopamine receptors (D4DR), almost exclusively present in the mesocortical and mesolimbic systems (O'Malley, K. L., Harmon, S., Tang, L., Todd, R. D., The rat dopamine D4 receptor: sequence, gene structure, and demonstration of expression in the cardiovascular system, *New Biol.*, 4, 137-46, 1992), are in the art known as modulators of emotion and cognition. D4DR agonistic activity gives a behavioural sensitisation; D4DR antagonistic activity leads to an emotion modulation (Svensson, T. H., Mathé, A. A., *Monoaminergic Transmitter Systems, Biological Psychiatry* (eds. D'Haenen, H., et al.), 45-66, 2002, John Wiley & Sons, Ltd). Data demonstrate that agonism of the dopamine D4 receptors play an important role in the induction of behavioral sensitization to amphetamine and accompanying adaptations in pre- and postsynaptic neural systems associated with the mesolimbocortical dopamine projections (D. L. Feldpausch et al.; *The Journal of Pharmacology and Experimental Therapeutics* Vol. 286, Issue 1, 497-508, July 1998).

Results suggest that the antagonisms of cortical D2 dopamine receptors are a common target of traditional and atypical antipsychotics for therapeutic action. Higher *in vivo* binding to the D2 receptors in the cortex than in the basal ganglia is suggested as an indicator of favorable profile for a putative antipsychotic compound (X. Xiberas and J.L. Martinot; *The British Journal of Psychiatry* (2001) 179: 503-508). Results show that dopamine D4 receptor antagonism in the brain does not result in the same neurochemical consequences (increased dopamine metabolism or hyperprolactinemia) observed with typical neuroleptics (Smita Patel et al., *The Journal of Pharmacology and Experimental Therapeutics* Vol. 283, Issue 2, 636-647, 1997). The selective D4 dopamine receptor antagonist L-745,870 was ineffective as an antipsychotic for the treatment of neuroleptic responsive patients with acute schizophrenia (Kramer, M.S. et al., *Arch. Gen. Psychiatry* 1997 Dec; 54(12):1080).

Finally, in the biological system, mental disorders are defined on other levels of abstraction than in the categorical and dimensional system. Structural pathology (e.g. amyloid plaques in Alzheimer Disease), etiology (e.g. HIV Dementia) and deviance from a physiological norm (e.g. reduced cerebral blood flow) are often used as indicative biological markers for a mental disorder. The underlying dysregulation of various neurotransmitter systems (glutaminergic, GABAergic, cholinergic, monoaminergic (nor-adrenergic, dopaminergic, serotonergic), etc.) is the in the art used model for the

explanation of the biological determinants of the clinical presentation of mental disturbances. It is known that the Serotonin 2A Receptor (5-HT2A receptor) - which is widespread in the Central Nervous System (CNS) - has a regulating role on the dysregulation of various neuro-transmitter systems. 5-HT2A agonism gives several 5 behavioural disturbances; 5-HT2A antagonism leads to a governance of mood, social behaviour, anxiety, cognitive function, stress, sleep functions, nociception, sexual functions, feeding and other aspects of behaviour (*J.E. Léysen (2004) 5-HT2 Receptors; Current Drug Targets – CNS & Neurological Disorders, 2004, 3, 11-26*).

Dysregulation of the HPA axis (hypothalamic - pituitary - adrenal axis) has frequently been 10 reported in patients with psychiatric disorders, and is among the most robustly demonstrated neurobiological changes among psychiatric patients (*D.A. Gutman and C.B. Nemeroff, Neuroendocrinology, Biological Psychiatry (eds D'Haenen, H., et al), 99, 2002, John Wiley & Sons, Ltd*). The resulting elevated plasma cortisol concentrations leads to an enhanced binding of serotonin for the 5-HT2A receptor (*E. A. Young, Mineralocorticoid 15 Receptor Function in Major Depression, Arch. Gen. Psychiatry, Jan 2003; 60: 24 - 28*) and thus agonism.

Additionally 5-HT2A antagonism gives a des-inhibiting of the inhibitory effect of the 5-HT2A receptor on (i) the 5-HT1A receptor stimulation by serotonin (*S. M. Stahl, Newer Antidepressants and Mood Stabilizers, Essential Psychopharmacology, 265 , University Press; 2 edition (June 15, 2000); ISBN: 0521646154*) and on (ii) the dopamine release in the mesocortical systems (*S. M. Stahl, Classical Antidepressants, Serotonin Selective and Noradrenergic Reuptake Inhibitors, Essential Psychopharmacology, 233 , University Press; 2 edition (June 15, 2000); ISBN: 0521646154*).

Clinical or real effectiveness of psychopharma is very rare via common pooping-out; many 25 treatment-refractory patients and up to half of patients fail to attain remission (*S. M. Stahl, Essential Psychopharmacology, Depression and Bipolar Disorders, 151, University Press; 2 edition (June 15, 2000); ISBN: 0521646154*). Implications of not attaining remission for Mental Disorders are increased relapse rates, continuing functional impairment and increased suicide rate (*S. M. Stahl, Essential Psychopharmacology, Depression and 30 Bipolar Disorders, 152 , University Press; 2 edition (June 15, 2000); ISBN: 0521646154*). Clinical causes of not attaining remission by the Current Psychopharmacological Compounds are inadequate early treatment, underlying emotion dysregulation (affecting instability – hypersensitivity – hyperesthesia – dissociative phenomena, etc.) and competitive antagonism. There is thus a growing need for a more efficient therapy and 35 more efficient, selective and efficacious medicaments for treating mental disorders.

Summary of the invention

The present invention relates to the use of compounds and pharmaceutical compositions having D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity for the treatment of the underlying emotion dysregulation of mental disorders (e.g. affecting instability – hypersensitivity – hyperesthesia – dissociative phenomena - etc.) and to methods entailing administering to a patient diagnosed as having a mental disorder a pharmaceutical composition containing (i) compounds having specific high selective D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic activity and (ii) a known medicinal compound and/or compositions of compounds. The combined D4 and 5-HT2A antagonistic, partial agonistic or inverse agonistic effects may reside within the same chemical or biological compound.

Taken into account the above mentioned (i) rare clinical or real effectiveness of psychotropics, (ii) the governance of the features and dysfunctions responsible - in a variable coincidentally – for the clinical state of the mental disorders by D4 dopamine receptor (D4DR) and 2A serotonin receptor (5-HT2A) antagonism and (iii) the fact that 5-HT2A antagonism gives a des-inhibiting of the inhibitory effect of the 5-HT2A receptor on (a) the 5-HT1A receptor stimulation by serotonin and on (b) the dopamine release in the mesocortical systems, the present invention relates to the use of a compound for the preparation of a medicament for treating a disease or disorder with an underlying emotion dysregulation, characterised in that said compound has (i) a selective affinity for the Dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors and wherein said compound is administered to a patient in a dose ranging between 5 and 15 mg of the active ingredient. Preferably, said compound is pipamperon.

In a preferred embodiment, in a mono therapeutic context, the invention relates to the use of a compound as defined above, preferably pipamperon, for preparing a medicament for treating a disease or disorder selected from the group comprising anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, cognitive disorders, impulse control disorders, pervasive development, attention-deficit and disruptive behaviour disorders, substance-related disorders,

personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational, identity, phase of life, academic problem, problems related to abuse or neglect.

According to a further embodiment the invention relates to the use of a first compound as defined above for the preparation of a medicament for treating a mental disease or disorder with an underlying emotion dysregulation whereby a second compound is administered simultaneously with, separate from or sequential to said first compound to augment the therapeutic effect of said second compound on said disease, or to provide a faster onset of the therapeutic effect of said second compound on said disease.

- 10 The mental diseases or disorders characterized by an underlying emotion dysregulation can be grouped into subclasses as follows: (i) non-cognitive mental disorders comprising mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment
- 15 disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect; (ii) cognitive diseases
- 20 comprising delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment
- 25 disorder, other cognitive disorders; (iii) pain disorders; and (iv) Parkinson Disease.

In a preferred embodiment, the first compound is administered daily at least one day before administering said second compound.

Preferably, said second compound is characterized by the physiological property of influencing positively the activity of the Central Nervous System.

- 30 The invention also relates to a method for preparing a compound having a selective D4 and 5-HT2A antagonist, reverse agonist or partial agonist activity comprising the following steps: (a) measuring the selective affinity of a test compound to the D4 receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the D4 receptor in respect to all the other D receptors, and measuring the selective efficacy of the

selected compound to the D4 receptor and selecting a compound which is a selective antagonist, inverse agonist or partial agonist of the D4 receptor; (b) measuring the selective affinity of a test compound to the 5-HT2A receptor and selecting a compound that has a pKi value equal to or greater than 8 towards the 5-HT2A receptor in respect to
5 all the other 5HT receptors, and measuring the selective efficacy of the selected compound to the 5-HT2A receptor and selecting a compound which is a selective antagonist, inverse agonist or partial agonist of the 5-HT2A receptor; (c) identifying a compound which is selected in (a) and (b), (d) preparing the compound identified in (c).

The invention further also relates to a compound prepared by the described method.

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Detailed description of the invention

The present inventors surprisingly found that compounds which have a high selective affinity towards the 5-HT2A receptor and which, at the same time have a high selective affinity towards the dopamine-4 (D4) receptor show an improved effect in treating
15 underlying emotion dysregulation of mental disorders.

The compounds according to the invention may be chemical or biological in nature, or may be chemically synthesised. Preferably, the compounds of the invention are provided as a pharmaceutically acceptable salt.

One example of such a compound which has both a selective affinity for the 5-HT2A
20 receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors, and a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors is pipamperon. Pipamperon is the conventional name given for the compound of the formula 1'-[3-(p-Fluorobenzoyl)propyl]-[1,4'-bipiperidine]-4'-carboxamide.
25 Pipamperon is also the active ingredient of for instance the commercially available Dipiperon (Janssen, Cilag B.V.).

Further, the present inventors surprisingly found that the dosage of active ingredient for pipamperon in treatment (in monotherapy as well as in combination therapy as described in more detail further) could be very low compared to conventionally used dosages.
30 Preferred dosages which, according to the invention, have been shown to be effective for treating these mental disorders, range between 5 and 15 mg per day or between 5 and 10 mg per day. More preferably, dosages of 5, 6, 7, 8, 9, 10, 11, 12, 13, 14 or 15 mg per day are used in treatment of the diseases of the invention. In conventional pipamperon

treatment, the active ingredient is available in tablets of 40 mg per tablet or in solutions of 2 mg per drop. Conventional usage of high doses ranging from 40 to 360 mg is prescribed. For instance, for children up to the age of 14, doses corresponding with 2 to 6 mg per kg body weight are conventionally prescribed. The high selective affinity of 5 pipamperon towards the 5-HT2A receptor and the D4 receptor is reflected in the low dosage which is needed for the treatment of the mental diseases listed below and also contributes to the efficacy of the treatment.

The mental disorders which can be treated using pipamperon in a mono therapy at such low doses are for instance anxiety disorders, eating disorders, premenstrual syndrome, 10 somatoform disorders, factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, cognitive disorders, impulse control disorders, pervasive development, attention-deficit and disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, 15 occupational, identity, phase of life, academic problem, problems related to abuse or neglect.

Mental disorders such as depression are commonly treated with serotonin re-uptake Inhibitors. Unfortunately, however, these compounds can give rise to side effects in use. Moreover, a substantial problem in most treatment of mental disorders is the non- 20 response to selective serotonin re-uptake inhibitors (SSRIs). Also the onset of the therapeutic effect can be delayed undesirable.

- A problem to be solved by the present invention is thus the provision of a more efficient therapy and efficient, highly selective and efficacious medicaments for treating mental disorders.
- 25 The inventors found that, for instance, the non-response to selective serotonin re-uptake inhibitors (SSRIs) in depression may be declared by (partial) inhibition of the 5-HT1A stimulation via 5-HT2A stimulation. Des-inhibition thereof via 5-HT2A antagonism seems to be an answer to this problem.
- The present inventors found that a simultaneous or foregoing treatment with a compound 30 having a high selective 5-HT2A antagonist, inverse agonist or partial agonist activity, could lead to a greater response towards, for instance, SSRIs. However, not all compounds exhibiting 5-HT2A antagonism are useful: competition between 5-HT2A stimulation via serotonin and 5-HT2A antagonism via the compound could be responsible for the lack of

more efficacy of compounds which have both a selective serotonin re-uptake inhibitory and 5-HT2A antagonist profile, such as trazodone and nefazodone.

- The present inventors further surprisingly found that a simultaneous or foregoing treatment with a compound having a high selective D4 antagonist, inverse agonist or 5 partial agonist activity in combination with a compound having a high selective 5-HT2A antagonist, inverse agonist or partial agonist activity could lead to a greater response towards, for instance, SSRIs, or any of the compounds listed in Table 6 or below. In addition, the inventors found that a combination treatment provides less residual symptoms and more remission relative to a mono therapy with these compounds.
- 10 As such, in a combination treatment, the doses of the compounds listed in Table 6 for treating patients with mental disorders may be decreased to about 10 - 90% of the conventional dose, preferably to about 20 - 80%, or 30 - 70%, or 40 - 60% or to about 50% of the conventional dose. Even if the administered dose of the compound is decreased in the combination therapy, the therapeutical effect may be sustained or 15 ameliorated relative to the conventional dose. The danger of side effects of a treatment with such compounds can be decreased or minimized in the combination therapy of the invention. In this regard, the term conventional dose refers to the dose used heretofor for a particular compound in treating patients with a mental disorder, for instance, according to the supplier's or physician's description or as listed in Table 6.
- 20 In this invention, the term "antagonist" refers to an interaction between chemicals in which one partially or completely inhibits the effect of the other, in particular agents having high affinity for a given receptor, but which do not activate this receptor.
- In this invention, the term "inverse agonist" refers to a ligand which produces an effect opposite to that of the agonist by occupying the same receptor.
- 25 In this invention, the term "agonist" relates to an agent which both binds to a receptor and has an intrinsic effect.
- In this invention, the term "partial agonist" relates to an agent with lower intrinsic activity than a full agonist, and which produces a lower maximum effect.
- The present inventors found that a compound which binds to the 5-HT2A receptor with a 30 pKi of at least 8 but for which the binding affinity, i.e. pKi, towards other 5HT receptors is less than 8 in combination with a high selective affinity for the D4 receptor, i.e. which bind to the D4 receptor with a pKi of at least 8 but for which the binding affinity, i.e. pKi, towards other dopamine receptors is less than 8 also show such an improved effect in treatment. These effects, i.e. D4 antagonism, inverse agonism or partial agonism and 5-

HT2A antagonism, inverse agonism or partial agonism, may reside in the same compound.

The term "other 5HT receptors" as used herein relate to for instance 5-HT1 receptors (e.g. 5-HT1A, 5-HT1B, 5-HT1D, 5-HT1E, 5-HT1F), 5-HT2B, 5-HT2C, 5-HT6 (rat) and 5-HT7 5 (rat).

By the expression "selective affinity for the 5-HT2A receptor" is meant that the receptor has a higher affinity for the 5-HT2A receptor than for other 5-HT receptors.

The expression "selective affinity for the D4 receptor" means that the receptor has a higher affinity for the dopamine D4 receptor than for other dopamine receptors.

10 The term "other dopamine receptors" are, for instance, D1, D2 and D3 dopamine receptors.

pKi values of test compounds for dopamine receptors as well as 5-HT2A receptors can be measured using commonly known assays.

15 Compounds which have a selective affinity for the D4 receptor preferably have a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors.

20 Preferably, the compounds of the invention which have a selective affinity for the 5-HT2A receptor (or the D4 receptor), are compounds which have a pKi value equal to or higher than 8 towards the 5-HT2A receptor and the D4 receptor, and less than 8 towards other 5-HT receptors or dopamine receptors, respectively, as can be measured, for instance by methods known in the art. For instance, the "NIMH Psychoactive Drug Screening Program (PDSP)" K_i database (<http://kidb.cwru.edu/nimh/5htp.php>), is a unique resource in the public domain which provides information on the abilities of drugs to interact with an expanding number of molecular targets. The PDSP K_i database serves as a data 25 warehouse for published and internally-derived pKi, or affinity, values for a large number of drugs and drug candidates at an expanding number of G-protein coupled receptors, ion channels, transporters and enzymes. The PDSP internet site also provides for commonly used protocols and assays for measuring pKi values of 5-HT and dopamine receptors.

30 A preferred example of a compound which has both a selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors, and a selective affinity for the D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other

Dopamine receptors and which is therefore useful in a combination therapy is pipamperon.

Table 1 illustrates the selective affinity of for instance pipamperon for the 5-HT2A and for the D4 receptor. In addition, Table 1 also illustrates the low or absence of affinity of 5 pipamperon for other receptors such as the adrenergic receptors Alpha 1A, Alpha 2A, Alpha 2B, Alpha 2C, Beta 1, Beta 2, and the histamine receptor H1. As such, treating patients with pipamperon will provide for less side effects which otherwise result from simultaneous stimulation of other receptors. Therefore, and according to preferred 10 embodiments, useful compounds according to the invention not only have a selective 5-HT2A and/or D4 affinity but also a low affinity for other receptors such as the adrenergic and histamine receptors.

The low dosage which can be used in pipamperon treatment, as already described earlier, contributes to the high selective affinity of the compound towards the 5-HT2A receptor and the D4 receptor and therefore also to the efficacy of the treatment.

15 The mental diseases or disorders characterized by an underlying emotion dysregulation can be grouped into subclasses as follows: (i) the non-cognitive mental disorders comprising mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, 20 adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect; (ii) cognitive 25 diseases comprising delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive 30 impairment disorder, other cognitive disorders; (iii) the pain disorders; and (iv) Parkinson Disease. In Table 5, this classification has been used for summarizing the diseases and disorders relative to known psychotropics. In Table 6, an overview of pharmacological grouping is provided, indicating the pharmaceutical profile numbering, the pharmaceutical profile, the main disease or disorder indication(s), the name of the compound, the dose 35 range, and the company producing or selling said compound.

These diseases and their diagnosis are very clearly defined in the "Diagnostic and Statistical Manual of Mental Disorders (DSM-IV)" published by the American Psychiatric Association. This manual sets forth diagnostic criteria, descriptions and other information to guide the classification and diagnosis of mental disorders and is commonly used in the field of neuropsychiatry. It is for instance available on the internet under:

<http://www.behavenet.com/capsules/disorders/dsm4tr.htm>.

The expression "non-cognitive diseases or disorders" used in some of the embodiments of the invention comprises the following group of diseases or disorders: mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problems, identity problem, phase of life problem, academic problem and problems related to abuse or neglect.

In other embodiments of the invention, the mental diseases or disorders that are characterized by an underlying emotion dysregulation belong to the group of pain disorders. For instance, the combination therapy with pipamperon is especially advantageous for management of acute pain in diseases such as, but not limited to, musculoskeletal diseases, rheumatoid arthritis, osteoarthritis and ankylosing spondylitis. For the classification of pain disorders, reference is also made to the DSM-IV where these disorders are clearly described in the section of somatoform disorders by way of internationally accepted diagnostic criteria.

In other embodiments of the invention, the 5-HT2A receptor and/or Dopamine-4 receptor antagonist, inverse agonist or partial agonist (e.g. pipamperon) is used in treatment of patients having neuro-degenerative diseases or disorders, or related cognitive diseases or disorders. The diseases or disorders of the present invention are characterized by an underlying degeneration of the Central Nervous System (CNS), preferably selected from the group consisting of, but not limited to, neurodegenerative diseases such as Parkinson Disease, and in other embodiments of the invention, selected from the group of (related) cognitive diseases or disorders such as Alzheimer Disease.

For instance, Parkinson Disease, which is a chronic progressive nervous disease chiefly of later life, is linked to decreased dopamine production in the substantia nigra and is

marked by tremor and weakness of resting muscles and by a shuffling gait. Dopamine agonists and even levodopa, widely used in Parkinson Disease, gives via a dopamine D4 receptor stimulation psychiatric manifestations. The induced release of serotonin acts via 5-HT2A stimulation as a "brake" on dopamine release (*Young B.K., Camicioli R., Ganzini L., Neuropsychiatric adverse effects of antiparkinsonian drugs. Characteristics, evaluation and treatment. Drugs Aging. 1997 May; 10(5): 367-83*). Because of the need of specific D4 and 5-HT2A antagonism in the treatment of Parkinson Disease with dopamine agonists and even levodopa, it seems reasonable to combine with a compound with a high selective D4 and 5-HT2A antagonism i.e. having merely no activity towards the other receptors especially the D2 receptor because of the primary need of the relieve of the excessive burden of remaining dopaminergic neurons. Therefore, the use of the so-called atypical anti-psychotics or serotonin-dopamine antagonists (SDAs) is absolutely contraindicated since their high affinity for the D2 receptor. Even the use of serotonin releasing compounds such as SSRIs in the absence of an effective 5-HT2A antagonism are counterproductive towards the Parkinson Disease symptoms although many Parkinson patients are in need for an antidepressant since major depression is a very common and disabling condition in this kind of patients.

The expression "(related) cognitive diseases or disorders" according to the invention comprises, the following group of diseases or disorders: delirium (F05), dementia (such as Alzheimer Disease (F00), vascular dementia (F01), dementia due to other general medical conditions (HIV disease (F02.4), head trauma (F06.8), Parkinson Disease (F02.3), Huntington Disease (F02.2), Pick Disease (F02.0), Creutzfeldt-Jacob Disease (F02.1) and other (F02.8)), substance-induced persisting dementia (F1x.6)), amnestic disorders due to a general medical condition (F06.8) or a substance-induced persisting amnestic disorder (F1x.6), mild cognitive impairment disorder (F06.7) and other cognitive disorders (F04). The above list of diseases is provided by way of example and is not intended to limit the invention.

For instance, Alzheimer Disease is a degenerative brain disease of unknown cause that is the most common form of dementia. Alzheimer Disease usually starts in late middle age or in old age as a memory loss for recent events spreading to memories for more distant events and progresses over the course of five to ten years to a profound intellectual decline characterized by dementia and personal helplessness. The disease is marked histologically by the degeneration of brain neurons especially in the cerebral cortex and by the presence of neurofibrillary tangles and plaques containing beta-amyloid. Because dopamine receptor D4 (DRD4) antagonism can inhibit the behavioral disturbances

- merely aggression and confusion - caused by the degeneration of dopamine D2 receptors (*Esiri, M.M., The basis for behavioural disturbances in dementia, J. Neurol. Neurosurg. Psychiatry, 1996; 61(2):127–130.*2) accompanied with Alzheimer disease and 5-HT2A antagonism has an important boosting effect towards the effect of cholinesterase 5 inhibitors such as used in the treatment by facilitating the affected dopamine release in the mesocortical dopamine pathways, a high selective D4/5-HT2A-antagonist would be a more preferable compound to combine with a cholinesterase inhibitor since this avoids the counteracting effect of the in the art used SDAs on the cognitive functioning by its dopamine receptor D2-antagonism.
- 10 These diseases and their diagnoses are very clearly defined in the "*International Statistical Classification of Diseases and Related Health Problems, 1989 Revision, Geneva, World Health Organization, 1992 (ICD-10)*". This manual sets forth diagnostic criteria, descriptions and other information to guide the classification and diagnosis of neurodegenerative disorders and is commonly used in the field of neurology. According to 15 the ICD-10 classification, the cognitive disorders are classified under several classes of disorders, i.e. dispersed under categories F00 to F19 (see above: respective classification between parentheses). Following the DSM classification, however, they are grouped in one class of diseases or disorders.
- The terms "treatment", "treating", and the like, as used herein include amelioration or 20 elimination of a developed mental disease or condition once it has been established or alleviation of the characteristic symptoms of such disease or condition. As used herein these terms also encompass, depending on the condition of the patient, preventing the onset of a disease or condition or of symptoms associated with a disease or condition, including reducing the severity of a disease or condition or symptoms associated 25 therewith prior to affliction with said disease or condition. Such prevention or reduction prior to affliction refers to administration of the compound or composition of the invention to a patient that is not at the time of administration afflicted with the disease or condition. "Preventing" also encompasses preventing the recurrence or relapse-prevention of a disease or condition or of symptoms associated therewith, for instance after a period of 30 improvement. It should be clear that mental conditions may be responsible for physical complaints. In this respect, the term "treating" also includes prevention of a physical disease or condition or amelioration or elimination of the developed physical disease or condition once it has been established or alleviation of the characteristic symptoms of such conditions.

As used herein, the term "medicament" also encompasses the terms "drug", "therapeutic", "potion" or other terms which are used in the field of medicine to indicate a preparation with therapeutic or prophylactic effect.

The present inventors not only found that the selective 5-HT2A and D4 antagonists,
5 inverse agonists or partial agonists have an effect in augmenting the therapeutic effect or
in providing a faster onset of the therapeutic effect of a diversity of other pharmaceutical
compounds, i.e. also named "second compounds" in the present invention, in the
treatment of specific diseases or disorders. A few examples of other pharmaceutical
compounds whose effects are augmented or where the onset of the effect is fastened
10 upon simultaneous or fore-going treatment with a selective 5-HT2A and D4 antagonist,
preferably pipamperon in a low dose, are nor-epinephrine re-uptake inhibitors, neuroleptic
agents, dopamine antagonists, or compounds used for treating or alleviating
musculoskeletal diseases or disorders. A further list of other pharmaceutical compounds
or second compounds useful according to the invention is provided in Table 5. It should
15 be clear, given the general applicable character of the invention, that this list of other
pharmaceutical compounds is very brief and that the invention should not be restricted to
the ones exemplified herein. It should be clear that in the present invention, pipamperon is
never to be seen as a "second compound".

According to the invention, it thus has been found that the compounds having a selective
20 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity as described above
are useful for augmenting the therapeutic effect of a second compound on a disease.

According to another embodiment of the invention, it has also been found that the
compounds having a selective 5-HT2A and D4 antagonist, inverse agonist or partial
agonist activity as described above are useful for providing a faster onset of the
25 therapeutic effect of a second compound on a disease.

From the above it should be clear that the selective 5-HT2A and D4 antagonist, inverse
agonist or partial agonist is also named 'the first compound' in the embodiments of the
invention.

According to the invention, when the 5-HT2A and D4 antagonist, inverse agonist or partial
30 agonist activity reside in separate compounds, the term "composition" may be used.
Compositions of the invention comprise a first element having (i) a selective affinity for the
D4 receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less
than 8 towards other dopamine receptors, and a second element having (ii) a selective

affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5-HT receptors.

The expression "the 5-HT2A and D4 antagonist, inverse agonist or partial agonist" is used herein to indicate a single compound having both activities or to indicate the composition 5 comprising the activities in separate elements.

It should be clear that when, in the present invention, a composition of separate elements is used instead of a single compound, this composition of separate elements may be used in combination with another, i.e. a second, compound to augment the therapeutic effect of the other, i.e. the second, compound on the same or another disease.

- 10 When the 5-HT2A and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements and the second compound are administered simultaneously, the compounds or active ingredients may be present in a single pharmaceutical composition or formulation. Alternatively the compounds or active ingredients are administered in separate pharmaceutical compositions or formulations for simultaneous or
- 15 15 separate use. The invention thus also relates to pharmaceutical compositions comprising pipamperon and a second compound of the invention and to the uses of these pharmaceutical compositions.

- When the 5-HT2A and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements of the invention are administered prior to the second compound 20 as defined, the 5-HT2A and D4 antagonist, inverse agonist or partial agonist or the composition comprising both elements is administered at least during 1 day prior to said second compound. Preferably, the 5-HT2A and D4 antagonist, inverse agonist or partial agonist (e.g. pipamperon) or the composition comprising both elements is administered for at least 1, 2, 3, 4, 5, 6, 7, 8, 9 or 10 days prior to the administration of the second 25 compound. Preferably, the 5-HT2A and D4 antagonist, inverse agonist or partial agonist (e.g. pipamperon) or the composition comprising both elements is administered for at least 2, 3, 4 or 5 weeks prior to the administration of the second compound, or even for at least 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11 or 12 months prior to the administration of the second compound.
- 30 According to a preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of citalopram or for providing a faster onset of the therapeutic effect of citalopram.

Citalopram or citalopram hydrobromide is a selective serotonin (5-hydroxytryptamine / 5-HT) re-uptake inhibitor (SSRI) and is the conventional name given for the compound of the formula (RS)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile hydro-bromide.

5

According to an embodiment, a daily dose of active ingredient of SSRI, preferably citalopram, ranges between 10 and 40 mg per day. Preferably, daily doses of active ingredient ranging between 20 and 30 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.

10

According to another preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of fluvoxamine or for providing a faster onset of the therapeutic effect of fluvoxamine.

15

Fluvoxamine or fluvoxamine maleate (luvox, fevarin) is a selective serotonin (5-HT) reuptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl) oxime maleate (1:1).

20

According to an embodiment, a daily dose of active ingredient of fluvoxamine maleate ranges between 100 and 300 mg per day. Preferably, daily doses of active ingredient ranging between 150 and 200 mg per day are administered. More preferably, a daily dose of 100, 150, 200, 250 or 300 mg per day is administered.

25

According to a preferred embodiment of the invention, the above described compounds or the composition comprising both elements having a 5-HT2A and D4 antagonist, inverse agonist or partial agonist activity are useful for augmenting the therapeutic effect of selegiline or for providing a faster onset of the therapeutic effect of selegiline.

Selegiline or L-deprenyl or phenylisopropyl methyl propynyl amine is a monoamine oxidase B inhibitor (MAO-B inhibitor) and is the conventional name given for the compound of the formula (R)-(-)-N, α-dimethyl-N-(2-propynyl) phenethylamine - HCl.

30

According to an embodiment, a daily dose of active ingredient of MAO-B inhibitor, preferably selegiline, ranges between 5 and 60 mg per day. Preferably, daily doses of active ingredient ranging between 20 and 40 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.

Most of the second compounds herein described are known in the art and may be used in doses according to the supplier's or physician's prescription, or may be used according to specific embodiments described herein.

- Also encompassed by the invention are pro-drugs to these second compounds or active metabolites of these compounds. For instance, for risperidone it is known that, among other products, bio transformation in the liver produces 9-hydroxyrisperidone, which is of the same pharmacological activity and intensity as parent risperidone. Therefore, also 9-hydroxyrisperidone, naturally produced or chemically synthesized may be used in the methods and uses according to the invention.
- 10 The term "active metabolite" as used herein relates to a therapeutically active compound produced by the metabolism of a parent drug. Drugs administered to treat diseases are usually transformed (metabolized) within the body into a variety of related chemical forms (metabolites), some of which may have therapeutic activity (an active metabolite).
- 15 The present invention also encompasses the use of these second compounds, administered in the form of a pharmaceutically acceptable salt in admixture with a suitable pharmaceutically acceptable excipient.
- 20 To prepare the pharmaceutical compositions, comprising the compounds or the combination of the first and second compound described herein, an effective amount of the active ingredients, in acid or base addition salt form or base form, is combined in admixture with a pharmaceutically acceptable carrier, which can take a wide variety of forms depending on the form of preparation desired for administration. These pharmaceutical compositions are desirably in unitary dosage form suitable, for administration orally, nasal, rectally, percutaneously, transdermally, by parenteral, intramuscular, intravascular injection or intrathecal administration. For example, in 25 preparing the compositions in oral dosage form, any of the usual pharmaceutical media may be employed, such as, for example, water, glycols, oils, alcohols and the like in the case of oral liquid preparations such as suspensions, syrups, elixirs and solutions; or solid carriers such as starches, sugars, kaolin, lubricants, binders, disintegrating agents and the like in the case of powders, pills, capsules and tablets. Because of their ease in 30 administration, tablets and capsules represent the most advantageous oral dosage unit form, in which case solid pharmaceutical carriers are obviously employed. For parenteral compositions, the carrier will usually comprise sterile water, at least in large part, though other ingredients, for example, to aid solubility, may be included.

The pharmaceutical compounds for treatment are intended for parenteral, topical, oral or local administration and generally comprise a pharmaceutically acceptable carrier and an amount of the active ingredient sufficient to reverse or prevent the bad effects of mental disorders. The carrier may be any of those conventionally used and is limited only by
5 chemico-physical considerations, such as solubility and lack of reactivity with the compound, and by the route of administration.

Examples of pharmaceutically acceptable acid addition salts for use in the present inventive pharmaceutical composition include those derived from mineral acids, such as hydrochloric, hydrobromic, phosphoric, metaphosphoric, nitric and sulfuric acids, and
10 organic acids, such as tartaric, acetic, citric, malic, lactic, fumaric, benzoic, glycolic, gluconic, succinic, p-toluenesulphonic acids, and arylsulphonic, for example.

The pharmaceutically acceptable excipients described herein, for example, vehicles, adjuvants, carriers or diluents, are well-known to those who are skilled in the art and are readily available to the public. It is preferred that the pharmaceutically acceptable carrier
15 be one that is chemically inert to the active compounds and one that has no detrimental side effects or toxicity under the conditions of use.

The following formulations for oral, aerosol, parenteral, subcutaneous, intravenous, intramuscular, interperitoneal, rectal, and vaginal administration are merely exemplary and are in no way limiting. Overall, the requirements for effective pharmaceutical carriers for
20 parenteral compositions are well known to those of ordinary skill in the art. See Pharmaceutics and Pharmacy Practice, J.B. Lippincott Company, Philadelphia, PA, Banker and Chalmers, eds., pages 238-250, (1982), and ASHP Handbook on Injectable Drugs, Toissel, 4th ed., pages 622-630 (1986). Topical formulations, including those that are useful for transdermal drug release, are well-known to those of skill in the art and are
25 suitable in the context of the present invention for application to skin.

Formulations suitable for oral administration require extra considerations considering the nature of the compounds and the possible breakdown thereof if such compounds are administered orally without protecting them from the digestive secretions of the gastrointestinal tract. Such a formulation can consist of (a) liquid solutions, such as an
30 effective amount of the compound dissolved in diluents, such as water, saline, or orange juice; (b) capsules, sachets, tablets, lozenges, and troches, each containing a predetermined amount of the active ingredient, as solids or granules; (c) powders; (d) suspensions in an appropriate liquid; and (e) suitable emulsions. Liquid formulations may include diluents, such as water and alcohols, for example, ethanol, benzyl alcohol, and the
35 polyethylene alcohols, either with or without the addition of a pharmaceutically acceptable

surfactant, suspending agent, or emulsifying agent. Capsule forms can be of the ordinary hard- or soft-shelled gelatin type containing, for example, surfactants, lubricants, and inert fillers, such as lactose, sucrose, calcium phosphate, and corn starch. Tablet forms can include one or more of lactose, sucrose, mannitol, corn starch, potato starch, alginic acid,
5 microcrystalline cellulose, acacia, gelatin, guar gum, colloidal silicon dioxide, croscarmellose sodium, talc, magnesium stearate, calcium stearate, zinc stearate, stearic acid, and other excipients, colorants, diluents, buffering agents, disintegrating agents, moistening agents, preservatives, flavoring agents, and pharmacologically compatible excipients. Lozenge forms can comprise the active ingredient in a flavor, usually sucrose
10 and acacia or tragacanth, as well as pastilles comprising the active ingredient in an inert base, such as gelatin and glycerin, or sucrose and acacia, emulsions, gels, and the like containing, in addition to the active ingredient, such excipients as are known in the art.

The compounds of the present invention, alone or in combination with other suitable components, can be made into aerosol formulations to be administered via inhalation. For
15 aerosol administration, the compounds are preferably supplied in finely divided form along with a surfactant and propellant. Typical percentages of compounds are 0.01%-20% by weight, preferably 1%-10%. The surfactant must, of course, be nontoxic, and preferably soluble in the propellant. Representative of such agents are the esters or partial esters of fatty acids containing from 6 to 22 carbon atoms, such as caproic, octanoic, lauric,
20 palmitic, stearic, linoleic, linolenic, olesteric and oleic acids with an aliphatic polyhydric alcohol or its cyclic anhydride. Mixed esters, such as mixed or natural glycerides may be employed. The surfactant may constitute 0.1%-20% by weight of the compounds, preferably 0.25-5%. The balance of the compounds is ordinarily propellant. A carrier can also be included as desired, e.g., lecithin for intranasal delivery. These aerosol
25 formulations can be placed into acceptable pressurized propellants, such as dichlorodifluoromethane, propane, nitrogen, and the like. They also may be formulated as pharmaceuticals for non-pressured preparations, such as in a nebulizer or an atomizer. Such spray formulations may be used to spray mucosa.

It will be understood that, apart from daily doses, the compounds can be administered by
30 other schedules. For instance, the present invention also contemplates depot injection, in which a long acting form of the active compound is injected into the body, such as the muscles. From there the active compound slowly enters the rest of the body, so one injection can last from 1 to 4 weeks or even multiple months. Other form of dosage administrations relate to "once-a-week" pills, in which the ingredient is slowly released

over a period of a week, and slow-release patches, e.g. a CDS (Continuous Delivery System), or Once-a-Day Transdermal Patches.

According to a further embodiment, the invention also relates to a method for preparing a compound or composition having a selective D4 and 5-HT2A antagonist, reverse agonist
5 or partial agonist. The invention also relates to the compounds prepared by the claimed method, with the proviso that said compound is not an already known compound, such as pipamperon.

It should be clear that the compounds and compositions described herein are useful for treating any patient in need thereof. As used herein the term "patient" is not restricted to
10 humans but also to other mammals, for instance, domestic animals which may also suffer from any form of a mental disease or disorder described herein.

The second compounds of the invention can be further grouped according to their pharmacological profile, which is summarized in Table 6.

The present invention is now described in more detail by the following embodiments. The
15 compounds belonging to different pharmacological profiles can be further grouped according to their action on the same pathway or system as follows.

1: combination therapy with a 5-HT (serotonin) reuptake enhancer

The mental disorders which can be treated using compounds having a high selective
20 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT (serotonin) reuptake enhancer, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment
25 disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep

- disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
5 from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
15 from or prior to the administration of a 5-HT (serotonin) reuptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT (serotonin) reuptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient
- 20 According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT (serotonin) reuptake enhancer compound is tianeptine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, tianeptine is to be administered in a daily dose ranging between 25 and 50 mg
25 of the active ingredient.
- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT (serotonin) reuptake enhancer, preferably tianeptine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined
30 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders,
35 adjustment disorders, impulse control disorders, substance related disorder, personality

disorder, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

A pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT (serotonin) reuptake enhancer is tianeptine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

10 2: combination therapy with a 5-HT1 autoreceptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1 autoreceptor agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

20

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1 autoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1 autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1 autoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1 autoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

10

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT1 autoreceptor agonist compound is sunepitron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

15 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1 autoreceptor agonist, preferably sunepitron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of
20 diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorder, personality disorder, antisocial behaviour, bereavement, occupational problem, problems related to
25 abuse or neglect and pain disorders.

3: combination therapy with a 5-HT1A (serotonin 1A receptor) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
30 with a 5-HT1A (serotonin 1A receptor) agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-
35 related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the

5 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational

10 problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in

15 that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention further also relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A (serotonin 1A receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A (serotonin 1A receptor) agonist compound, further characterized in that

20 pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT1A (serotonin 1A receptor) agonist compound is chosen from

30 the group consisting of MN-305, zolospirone, xaliproden, VPI-013 (also known as OPC-14523), tandospirone, sarizotan, PRX-00023, metanospirone, lesopitron, gepirone, flesinoxan, EMD 68843, buspirone, bupropion (preferably controlled release formulation) and alnespirone, preferably xaliproden, sarizotan, gepirone, flesinoxan and bupropion (preferably controlled release formulation) or a pro-drug or an active metabolite thereof, or

35 a pharmaceutically acceptable salt thereof. More preferably, said 5-HT1A (serotonin 1A receptor) agonist is xaliproden and is to be administered in a daily dose ranging between

1 and 2 mg of the active ingredient. Even more preferably, said 5-HT1A (serotonin 1A receptor) agonist is bupropion (controlled release formulation) and is to be administered in a daily dose ranging between 150 and 450 mg of the active ingredient. Even more preferably, said 5-HT1A (serotonin 1A receptor) agonist is gepirone and is to be
5 administered in a daily dose, ranging between 20 and 80 mg of the active ingredient per day.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1A (serotonin 1A receptor) agonist, preferably chosen from the group
10 consisting of MN-305, zolospirone, xaliproden, VPI-013 (also known as OPC-14523), tandospirone, sarizotan, PRX-00023, metanospirone, lesopitron, gepirone, flesinoxan, EMD 68843, buspirone, bupropion (preferably controlled release formulation) and alnespirone, more preferably xaliproden, sarizotan, gepirone, flesinoxan and bupropion
15 (preferably controlled release formulation), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative
20 disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

- 25 The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT1A (serotonin 1A receptor) agonist is xaliproden, preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.
- 30 The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT1A (serotonin 1A receptor) agonist is bupropion (controlled release formulation), preferably provided in a unitary dose of between 150 and 450 mg of the active ingredient.

The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT1A (serotonin 1A receptor) agonist is gepirone, preferably provided in a unitary dose of between 20 and 80 mg of the active ingredient.

5

4: combination therapy with a 5-HT1A (serotonin 1A receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1A (serotonin 1A receptor) antagonist compound, are chosen from the group 10 of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect

15

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating 20 disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt 25 thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1A antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT1A antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT1A antagonist compound is chosen from the group consisting of robalzotan tartrate hydrate and NAD299 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

35

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT1A antagonist, preferably chosen from the group consisting of robalzotan tartrate hydrate and NAD299, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, 5 separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, adjustment disorders, impulse control 10 disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

5: combination therapy with a 5-HT1B (serotonin 1B receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective 15 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT1B (serotonin 1B receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, 20 adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically 25 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, 30 adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT1B antagonist compound to augment the therapeutic effect or to 35 provide a faster onset of the therapeutic effect of said 5-HT1B antagonist compound,

further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above,
5 wherein said 5-HT1B antagonist compound is chosen from the group consisting of elzasonan, AZD1134 and AR-A2, preferably elzasonan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
10 and (b) a 5-HT1B antagonist, preferably chosen from the group consisting of elzasonan, AZD1134 and AR-A2, preferably elzasonan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation
15 of a non-cognitive mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related
20 to abuse or neglect.

6: combination therapy with a 5-HT2B (serotonin 2B receptor) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
25 with a 5-HT2B (serotonin 2B receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to
30 abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating

disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2B antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT2B antagonist compound is agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, agomelatine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT2B antagonist, preferably agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour,

bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

A pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT2B antagonist is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

7: combination therapy with a 5-HT2C (serotonin 2C receptor) antagonist compound

- 10 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT2C (serotonin 2C receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2C antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2C antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT2C antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT2C
5 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said 5-HT2C antagonist compound is chosen from the group consisting of
10 SB 243213 and agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, agomelatine is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
15 and (b) a 5-HT2C antagonist, preferably chosen from the group consisting of SB 243213 and agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood
20 disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorder, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

25 The present invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT2C antagonist is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

30 8: combination therapy with a 5-HT3 (serotonin 3 receptor) antagonist compound
The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a 5-HT3 (serotonin 3 receptor) antagonist compound, are substance-related
35 disorders.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance-related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with,
- 5 separate from or prior to the administration of a 5-HT3 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT3 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT3 antagonist compound is ondansetron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, ondansetron is to be administered in a daily dose ranging between 8 and 32 mg of the active ingredient.
- 15 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT3 antagonist, preferably ondansetron or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation
- 20 of substance-related disorders.
- The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said 5-HT3 antagonist is ondansetron, preferably provided in a unitary dose
- 25 of between 8 and 32 mg of the active ingredient.
- 9: combination therapy with a 5-HT6 (serotonin 6 receptor) antagonist compound
- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
- 30 with a 5-HT6 (serotonin 6 receptor) antagonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic
- 35 disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a 5-HT6 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 5-HT6 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said 5-HT6 antagonist compound is chosen from the group consisting of SB-271046, 742457 and 271046 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a 5-HT6 antagonist, preferably chosen from the group consisting of SB-271046, 742457 and 271046 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

10: combination therapy with an acetylcholinesterase inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an acetylcholinesterase inhibitor compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an acetylcholinesterase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said acetylcholinesterase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said acetylcholinesterase inhibitor compound is chosen from the group consisting of tacrine, rivastigmine tartrate, rivastigmine, physostigmine, phenserine tartrate, metrifonate, huperzine A, galantamine (preferably extended release formulation), donepezil, dichlorvos and anseculin hydrochloride, preferably tartrate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, rivastigmine tartrate is to be administered in a daily dose ranging between 3 and 12 mg of the active ingredient. Preferably, phenserine tartrate is to be administered in a daily dose ranging between 20 and 30 mg of the active ingredient. Preferably, galantamine

(extended release formulation) is to be administered in a daily dose ranging between 8 and 24 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
5 and (b) an acetylcholinesterase inhibitor, preferably chosen from the group consisting of tacrine, rivastigmine tartrate, rivastigmine, physostigmine, phenserine tartrate, metrifonate, huperzine A, galantamine (preferably extended release formulation), donepezil, dichlorvos and anseculin hydrochloride, preferably tartrate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined
10 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,
15 dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein
20 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is rivastigmine tartrate, preferably provided in a unitary dose of between 3 and 12 mg of the active ingredient.

The invention further relates to a pharmaceutical composition as described above wherein
25 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is phenserine tartrate, preferably provided in a unitary dose of between 20 and 30 mg of the active ingredient.

In addition, the invention relates to a pharmaceutical composition as described above
30 wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said acetylcholinesterase inhibitor is galantamine (preferably extended release formulation), preferably provided in a unitary dose of between 8 and 24 mg of the active ingredient.

11: combination therapy with an adenosine A2a receptor antagonist compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an adenosine A2a receptor antagonist compound, is Parkinson disease.

5

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate 10 from or prior to the administration of an adenosine A2a receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adenosine A2a receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

According to a preferred embodiment, the invention relates to the use as described above, wherein said adenosine A2a receptor antagonist compound is KW-6002 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, KW-6002 is to be administered in a daily dose ranging between 40 and 80 mg of the 20 active ingredient

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an adenosine A2a receptor antagonist, preferably KW-6002 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined 25 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient 30 and wherein said acetylcholinesterase inhibitor is KW-6002, preferably provided in a unitary dose of between 40 and 80 mg of the active ingredient.

12: combination therapy with an adrenergic transmitter releaser

The mental disorders which can be treated using compounds having a high selective 35 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an adrenergic transmitter releaser, are chosen from the group of diseases or

disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem,
5 problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the
10 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that
15 pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging
20 between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
25 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an adrenergic transmitter releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said adrenergic transmitter releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
30 ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said adrenergic transmitter releaser compound is pipoxazole or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably,
35 pipoxazole is to be administered in a daily dose ranging between 30 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an adrenergic transmitter releaser, preferably pipoxazole, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said adrenergic transmitter releaser is pipoxazole, preferably provided in a unitary dose of between 30 and 60 mg of the active ingredient

13: combination therapy with an alpha 1 adrenoreceptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an alpha 1 adrenoreceptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose
5 ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
10 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
15 ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said
20 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 1 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 1 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
25 ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said alpha 1 adrenoreceptor antagonist compound is chosen from the group consisting of SDZ NVI 085 and flesinoxan or a pro-drug or an active metabolite
30 thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an alpha 1 adrenoreceptor antagonist, preferably chosen from the group consisting of SDZ NVI 085 and flesinoxan or a pro-drug or an active metabolite thereof, or
35 a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental

disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and Parkinson disease.

14: combination therapy with an alpha 2 adrenoreceptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an alpha 2 adrenoreceptor antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an alpha 2 adrenoreceptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said
5 alpha 2 adrenoreceptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described
10 above, wherein said alpha 2 adrenoreceptor antagonist compound is chosen from the group consisting of UK-14304, sunepitron, mirtazepine, idazoxan, fluparoxan, A75200 and (R)-A 75200, preferably sunepitron or idazoxan, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, idazoxan is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.
15

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an alpha 2 adrenoreceptor antagonist, preferably chosen from the group consisting of UK-14304, sunepitron, mirtazepine, idazoxan, fluparoxan, A75200 and (R)-A 75200, preferably sunepitron or idazoxan, or a pro-drug or an active metabolite thereof,
20 or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious
25 disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

30 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said alpha 2 adrenoreceptor antagonist is Idazoxan, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.

15: combination therapy with an AMPA receptor mediator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an AMPA (alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate) receptor mediator compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-induced disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or

25 neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging

30 between 5 and 15 mg of the active ingredient.

35

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an AMPA receptor mediator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said AMPA receptor mediator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said AMPA receptor mediator compound is chosen from the group consisting of ampakine ORG 24448/CX-619, ampakine CX-717, ampakine CX-691 and ampakine CX-516, preferably ampakine ORG 24448/CX-619, ampakine CX-717 or ampakine CX-691, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

30 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an AMPA receptor mediator, preferably chosen from the group consisting of ampakine ORG 24448/CX-619, ampakine CX-717, ampakine CX-691 and ampakine CX-

516, preferably ampakine ORG 24448/CX-619, ampakine CX-717 or ampakine CX-691, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is
5 chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality
10 disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,
15 dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

16: combination therapy with an amphetamine compound

20 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an amphetamine compound, are attention-deficit disorders.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention deficit disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an amphetamine compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said
30 amphetamine compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said amphetamine compound is methylphenidate (preferably administered by a
35 transdermal system) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an amphetamine, preferably methylphenidate (preferably administered by a transdermal system) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of attention deficit disorders.

17: combination therapy with an amyloid aggregation-inhibitor compound

- 10 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an amyloid aggregation-inhibitor compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia
- 15 due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.
- 20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head
- 25 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered
- 30 simultaneously with, separate from or prior to the administration of an amyloid aggregation-inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said amyloid aggregation-inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said amyloid aggregation-inhibitor compound is chosen from the group consisting of APAN and Alzhemed, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, Alzhemed is to be administered in a 5 daily dose of between 200 and 300 mg of the active ingredient

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an amyloid aggregation-inhibitor, preferably chosen from the group consisting of APAN and Alzhemed, or a pro-drug or an active metabolite thereof, or a pharmaceutically 10 acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia 15 due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

20 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said amyloid aggregation-inhibitor is Alzhemed, preferably provided in a unitary dose of between 200 and 300 mg of the active ingredient.

25 **18: combination therapy with an androgen receptor modulator compound**

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an androgen receptor modulator compound, are sexual and gender identity disorders.

30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an androgen receptor 35 modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said androgen receptor modulator compound, further characterized in

that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said androgen receptor modulator compound is LGD2226 or a pro-drug or an 5 active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an androgen receptor modulator, preferably LGD2226 or a pro-drug or an active 10 metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of sexual and gender identity disorders.

19: combination therapy with an beta 3 adrenoreceptor agonist

The mental disorders which can be treated using compounds having a high selective 15 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an beta 3 adrenoreceptor agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment 20 disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically 25 acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep 30 disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide 35 a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound,

further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an beta 3 adrenoreceptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said beta 3 adrenoreceptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said beta 3 adrenoreceptor agonist compound is SR 58611 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a beta 3 adrenoreceptor agonist, preferably SR 58611 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

30 20: combination therapy with a calcium channel modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a calcium channel modulator compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick

Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson disease.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head
10 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered
15 simultaneously with, separate from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
20
The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
25 from or prior to the administration of a calcium channel modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said calcium channel modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
30 According to a preferred embodiment, the invention relates to the uses as described above, wherein said calcium channel modulator compound is chosen from the group consisting of safinamide and MEM 1003, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
35

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a calcium channel modulator, preferably chosen from the group consisting of safinamide and MEM 1003, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson disease.

21: combination therapy with a cannabinoid receptor 1 (CB1) antagonist

15 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a cannabinoid receptor 1 (CB1) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative 20 disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, psychotic 30 disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem 35 and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate

from or prior to the administration of a cannabinoid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabinoid receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active 5 ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said 10 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabinoid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabinoid receptor 1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active 15 ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said 20 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cannabinoid receptor 1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cannabinoid receptor 1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active 25 ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said cannabinoid receptor antagonist compound is SR 141716 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

30 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a cannabinoid receptor antagonist, preferably SR 141716 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying 35 emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic

disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions,
5 malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

22: combination therapy with a cathepsin K inhibitor compound

The mental disorders which can be treated using compounds having a high selective
10 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a cathepsin K inhibitor compound, are pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
15 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a cathepsin K inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said cathepsin K inhibitor compound, further characterized in that pipamperon is to be administered to a
20 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said cathepsin K inhibitor compound is 462795 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

25 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a cathepsin K inhibitor, preferably 462795 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation
30 of pain disorders.

23: combination therapy with a choline uptake enhancer compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
35 with a choline uptake enhancer compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia,

vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a choline uptake enhancer compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said choline uptake enhancer compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said choline uptake enhancer compound is MKC-231 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, MKC-231 is to be administered in a daily dose of between 20 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a choline uptake enhancer, preferably MKC-231 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic

disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein
5 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said choline uptake enhancer is MKC-231, preferably provided in a unitary dose of between 20 and 160 mg of the active ingredient.

24: combination therapy with a COX-2 inhibitor compound

10 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a COX-2 inhibitor compound, are pain disorders.

15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a COX-2 inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said COX-2
20 inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said COX-2 inhibitor compound is chosen from the group consisting of
25 valdecoxib, rofecoxib, parecoxib, etoricoxib, COX 189, celecoxib and ABT-963, preferably parecoxib, etoricoxib or COX 189, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, parecoxib is to be administered in a daily dose of between 20 and 80 mg of the active ingredient. Preferably, etoricoxib is to be administered in a daily dose of between 20 and 120 mg of the active ingredient.
30 Preferably, COX 189 is to be administered in a daily dose of between 100 and 800 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a COX-2 inhibitor, preferably chosen from the group consisting of valdecoxib, rofecoxib, parecoxib, etoricoxib, COX 189, celecoxib and ABT-963, preferably parecoxib, etoricoxib or COX 189, or a pro-drug or an active metabolite thereof, or a

pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain disorders.

- 5 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is parecoxib, preferably provided in a unitary dose of between 20 and 80 mg of the active ingredient.
- 10 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is etoricoxib, preferably provided in a unitary dose of between 20 and 120 mg of the active ingredient.
- 15 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-2 inhibitor is COX 189, preferably provided in a unitary dose of between 100 and 800 mg of the active ingredient
- 20 **25: combination therapy with a COX-inhibiting nitric oxide donator (CINOD) compound**
The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a COX-inhibiting nitric oxide donator (CINOD) compound, are pain disorders.
- 25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a COX-inhibiting nitric oxide donator (CINOD)
- 30 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said COX-inhibiting nitric oxide donator (CINOD) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 35 According to a preferred embodiment, the invention relates to the use as described above, wherein said COX-inhibiting nitric oxide donator (CINOD) compound is chosen from the

group consisting of AZD4717 and AZD3582 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, AZD3582 is to be administered in a daily dose ranging between 93.75 and 750 mg of the active ingredient

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a COX-inhibiting nitric oxide donor (CINOD), preferably chosen from the group consisting of AZD4717 and AZD3582 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of pain
10 disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said COX-inhibiting nitric oxide donor (CINOD) is AZD3582, preferably
15 provided in a unitary dose of between 93.75 and 750 mg of the active ingredient.

26: combination therapy with a CRF1 (corticoid-releasing factor receptor 1) antagonist

- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
20 with a CRF1 (Corticotropin-Releasing Factor receptor 1) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders,
25 personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders,
30 personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt
35

thereof is administered simultaneously with, separate from or prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 5 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said 10 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a CRF1 antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said CRF1 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15 According to a preferred embodiment, the invention relates to the uses as described above, wherein said CRF1 antagonist compound is chosen from the group consisting of R121919, NBI-34041, elzasonan, CP-448,187, CP-154-526, AAG 561 and 723620, preferably R121919, elzasonan or AAG 561, or a pro-drug or an active metabolite thereof, 20 or a pharmaceutically acceptable salt thereof. Preferably, R121919 is to be administered in a daily dose of between 5 and 80 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a CRF1 antagonist, preferably chosen from the group consisting of R121919, NBI- 25 34041, elzasonan, CP-448,187, CP-154-526, AAG 561 and 723620, preferably R121919, elzasonan or AAG 561, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, 30 separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said CRF1 antagonist is R121919, preferably provided in a unitary dose of between 5 and 80 mg of the active ingredient.

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27: combination therapy with a D1 (dopamine 1) receptor agonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a D1 (dopamine 1) receptor agonist, are chosen from the group of diseases or 10 disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or 15 said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active 20 ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said 25 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D1 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D1 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30

According to a preferred embodiment, the invention relates to the uses as described above, wherein said D1 receptor agonist compound is DAS-431 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

35 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D1 receptor agonist, preferably DAS-431 or a pro-drug or an active metabolite

thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

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28: combination therapy with D2 (dopamine 2) receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with D2 (dopamine 2) receptor antagonist, are chosen from the group of diseases or 10 disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, 15 bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 20 emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, 25 personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or 30 to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 35 emotion dysregulation of pain disorders, characterized in that pipamperon or said

pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a 5 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said 10 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D2 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D2 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15 According to a preferred embodiment, the invention relates to the uses as described above, wherein said D2 receptor antagonist compound is chosen from the group consisting of bifeprunox and amisulpride, preferably bifeprunox, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

20 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D2 receptor antagonist, preferably chosen from the group consisting of bifeprunox and amisulpride, preferably bifeprunox, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for 25 simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological 30 factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

29: combination therapy with D3 (dopamine 3) receptor antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with D3 (dopamine 3) receptor antagonist, are chosen from the group of diseases or 5 disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, 10 occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium and Parkinson disease

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 15 emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, 20 psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster 25 onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 30 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor 35 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of delirium, characterized in that pipamperon or said 5 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a D3 receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate 15 from or prior to the administration of a D3 receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said D3 receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 20 According to a preferred embodiment, the invention relates to the uses as described above, wherein said D3 receptor antagonist compound is chosen from the group consisting of BSF-201640 and PD 58491, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- 25 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D3 receptor antagonist, preferably chosen from the group consisting of BSF- 30 201640 and PD 58491, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of 35 psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders, delirium and Parkinson disease.

30: combination therapy with a DA (dopamine) uptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy 5 with a DA (dopamine) uptake inhibitor, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 10 emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a DA uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA uptake inhibitor compound, further characterized in that pipamperon is to be administered 15 to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said 20 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a DA uptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said DA uptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25 According to a preferred embodiment, the invention relates to the uses as described above, wherein said DA uptake inhibitor compound is chosen from the group consisting of safinamide and GBR 12909, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

30 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a D2 receptor antagonist, preferably chosen from the group consisting of safinamide and GBR 12909, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, 35 separate or sequential use for treating the underlying emotion dysregulation of a mental

disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

31: combination therapy with an dopamine (receptor) agonist

5 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an dopamine (receptor) agonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative 10 disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative 20 disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 25 dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said 35 dopamine (receptor) agonist compound, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine (receptor) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine (receptor) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said dopamine (receptor) agonist compound is chosen from the group consisting of sumanirole, SLV 308, sarizotan, S32504, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation), pramipexole, DAB452, cabergoline, bromocriptine, alaptide, cabergoline, lisuride, preferably sumanirole, rotigotine (preferably a Once-a-Day Transdermal Patch), pergolide or ropinirole HCL (preferably controlled-release formulation), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, sumanirole is to be administered in a daily dose of between 4 and 16 mg of the active ingredient. Preferably, rotigotine (Once-a-Day Transdermal Patch) is to be administered in a daily dose of between 4.5 and 13.5 mg of the active ingredient. Preferably, ropinirole HCL (controlled-release formulation) is to be administered in a daily dose of between 0.75 and 24 mg of the active ingredient. Preferably, pergolide is to be administered in a daily dose of between 0.5 and 10 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a dopamine (receptor) agonist, preferably chosen from the group consisting of sumanirole, SLV 308, sarizotan, S32504, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation), pramipexole, DAB452, cabergoline, bromocriptine, alaptide, cabergoline, lisuride and pergolide, more preferably sumanirole, rotigotine (preferably a Once-a-Day Transdermal Patch), ropinirole HCL (preferably controlled-release formulation) or pergolide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a

combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
5 factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein
10 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is sumanirole, preferably provided in a unitary dose of between 4 and 16 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein
15 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is rotigotine (Once-a-Day Transdermal Patch), preferably provided in a unitary dose of between 4.5 and 13.5 mg of the active ingredient.

20 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is ropinirole HCL (controlled-release formulation), preferably provided in a unitary dose of between 0.75 and 24 mg of the active ingredient

25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is pergolide, preferably provided in a unitary dose of between 0.5 and 10 mg of the active ingredient

30 32: combination therapy with a compound activating ERK (extracellular signal-related kinase)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
35 with a compound that activates ERK (extracellular signal-related kinase), are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced

persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound that activates ERK (extracellular signal-related kinase) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound that activates ERK (extracellular signal-related kinase), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound that activates ERK (extracellular signal-related kinase) is CPI-1189 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, CPI-1189 is to be administered in a daily dose of between 50 and 100 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound that activates ERK (extracellular signal-related kinase), preferably CPI-1189 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease,

dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound that activates ERK (extracellular signal-related kinase) is CPI-1189, preferably provided in a unitary dose of between 50 and 100 mg of the active ingredient.

33: combination therapy with a GABA (gamma-aminobutyric acid) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA (gamma-aminobutyric acid) agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA agonist compound, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above,
5 wherein said GABA agonist compound is nefiracetam or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and
10 (b) a GABA agonist, preferably nefiracetam or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to
15 Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

20 **34: combination therapy with a GABA-A agonist compound**

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA-A (gamma-aminobutyric acid receptor A) agonist compound, are sleep disorders.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of sleep disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA-A agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-A agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35 According to a preferred embodiment, the invention relates to the use as described above, wherein said GABA-A agonist compound is gaboxadol or a pro-drug or an active

metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, gaboxadol is to be administered in a daily dose of between 5 and 20 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
5 and (b) an GABA-A agonist, preferably gaboxadol or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of sleep disorders.

10 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A agonist is Gaboxadol, preferably provided in a unitary dose of between 5 and 20 mg of the active ingredient.

15 35: combination therapy with a GABA-A modulator compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA-A (gamma-aminobutyric acid receptor A) modulator compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, 20 premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious 30 disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA-A modulator 35 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-A modulator compound, further characterized in that pipamperon is to

be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above,
5 wherein said GABA-A modulator compound is chosen from the group consisting of zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), SL 65.1498, SEP174559, pagoclone, NGD 96-3, indiplon, eszopiclone, CP-730,330 (NGD 96-3) and ocinaplon, preferably zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation),
10 pagoclone, indiplon or eszopiclone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, zolpidem MR sustained-release version is to be administered in a daily dose of between 10 and 20 mg of the active ingredient. Preferably, zaleplon extended-release is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient. Preferably, pagoclone is to be
15 administered in a daily dose ranging between 7.5 and 60 mg of the active ingredient. Preferably, indiplon is to be administered in a daily dose of between 10 and 20 mg of the active ingredient. Preferably, eszopiclone is to be administered in a daily dose of between 2 and 3 mg of the active ingredient. Preferably, ocinaplon is to be administered in a daily dose of between 10 and 60 mg of the active ingredient.

20 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GABA-A modulator, preferably chosen from the group consisting of zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), SL 65.1498, SEP174559, pagoclone, indiplon, eszopiclone, CP-730,330
25 (NGD 96-3) and ocinaplon, preferably zolpidem (preferably MR sustained-release version), zaleplon (preferably extended-release formulation), pagoclone, NGD 96-3, indiplon or eszopiclone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental
30 disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse
35 or neglect.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is zolpidem MR sustained-release version, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

5

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is zaleplon extended-release, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

10

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is Pagoclone, preferably provided in a unitary dose of between 7.5 and 60 mg of the active ingredient.

15

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is indiplon, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

20

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is eszopiclone, preferably provided in a unitary dose of between 2 and 3 mg of the active ingredient.

25

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GABA-A modulator is ocinaplon, preferably provided in a unitary dose of between 10 and 60 mg of the active ingredient.

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36: combination therapy with a GABA-B antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a GABA-B (gamma-aminobutyric acid receptor B) antagonist compound, are chosen

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from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious

disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious
10 disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GABA-B antagonist
15 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GABA-B antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 20 According to a preferred embodiment, the invention relates to the use as described above wherein said GABA-B antagonist compound is AVE 7398 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
25 and (b) a GABA-B antagonist, preferably AVE 7398 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform
30 disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

37: combination therapy with a Glial-cell Line Derived Neurotrophic Factor compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a Glial-cell Line Derived Neurotrophic Factor compound, is Parkinson disease.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate 10 from or prior to the administration of a Glial-cell Line Derived Neurotrophic Factor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said Glial-cell Line Derived Neurotrophic Factor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

According to a preferred embodiment, the invention relates to the use as described above, wherein said Glial-cell Line Derived Neurotrophic Factor compound is GDNF or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, GDNF is to be administered in a daily dose ranging between 3.75 and 30 mg of the active 20 ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a Glial-cell Line Derived Neurotrophic Factor, preferably GDNF or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined 25 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient 30 and wherein said Glial-cell Line Derived Neurotrophic Factor is GDNF, preferably provided in a unitary dose of between 3.75 and 30 mg of the active ingredient.

38: combination therapy with a glucocorticoid synthesis inhibitor compound

The mental disorders which can be treated using compounds having a high selective 35 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy

with a glucocorticoid synthesis inhibitor compound, are chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glucocorticoid synthesis inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glucocorticoid synthesis inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glucocorticoid synthesis inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said glucocorticoid synthesis inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said glucocorticoid synthesis inhibitor compound is metyrapone or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a glucocorticoid synthesis inhibitor, preferably metyrapone or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of substance related disorders and Parkinson disease.

39: combination therapy with a glutamate receptor antagonist compound

- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a glutamate receptor antagonist compound, are chosen from the group of diseases or
- 5 disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment
- 15 disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glutamate receptor antagonist compound to augment the therapeutic effect or to provide a
- 20 faster onset of the therapeutic effect of said glutamate receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a glutamate receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said

25 glutamate receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described

30 above, wherein said glutamate receptor antagonist compound is LY354740 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a glutamate receptor antagonist, preferably LY354740 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, 10 occupational problem, problems related to abuse or neglect and pain disorders.

40: combination therapy with an GPCR (G-protein-coupled receptor) modulator

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy 15 with an GPCR (G-protein-coupled receptor) modulator, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality 20 disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 25 emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, 30 personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GPCR modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GPCR modulator compound, further characterized 35 in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said 5 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GPCR modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GPCR modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 According to a preferred embodiment, the invention relates to the uses as described above, wherein said GPCR modulator compound is R1204 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- 15 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GPCR modulator, preferably R1204 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders 20 consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain 25 disorders.

41: combination therapy with an GR (glucocorticoid receptor) antagonist

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy 30 with an GR (glucocorticoid receptor) antagonist, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, 35 bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the
5 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse
10 or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15
15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
20 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a GR antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said GR antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25 According to a preferred embodiment, the invention relates to the use as described above, wherein said GR antagonist compound is chosen from the group consisting of ORG 34517/34850 and mifepristone, preferably mifepristone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, mifepristone
30 is to be administered in a daily dose of between 600 and 1200 mg of the active ingredient

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a GR antagonist, preferably chosen from the group consisting of ORG 34517/34850 and mifepristone, preferably mifepristone, or a pro-drug or an active
35 metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders,
5 adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein
10 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said GR antagonist is Mifepristone, preferably provided in a unitary dose of between 600 and 1200 mg of the active ingredient.

42: combination therapy with a histamine H3-receptor antagonist

15 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a histamine H3-receptor antagonist, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia
20 due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head
30 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered
35 simultaneously with, separate from or prior to the administration of a histamine H3-receptor antagonist compound to augment the therapeutic effect or to provide a faster

onset of the therapeutic effect of said histamine H3-receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 5 According to a preferred embodiment, the invention relates to the uses as described above, wherein said histamine H3-receptor antagonist compound is chosen from the group of compounds consisting of ABT-834 and ABT-239, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- 10 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a histamine H3-receptor antagonist, preferably chosen from the group consisting of ABT-834 and ABT-239 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.
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43: combination therapy with a hormonal substance

- 25 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a hormonal substance, are chosen from the group of diseases or disorders consisting of premenstrual syndrome and sexual and gender identity disorders.

- 30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of premenstrual syndrome and sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a hormonal substance to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said hormonal substance, further characterized in
- 35

that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said hormonal substance is chosen from the group consisting of a testosterone transdermal spray, a testosterone gel, a female testosterone patch, synthetic conjugated estrogen A, methyltestosterone, a estrogens/methyltestosterone and a drosiperone/ethinyl estradiol composition, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said hormonal substance is synthetic conjugated estrogen A and is to be administered in a daily dose ranging between 0.075 and 0.6 mg of the active ingredient. More preferably, said hormonal substance is a drosiperone/ethinyl estradiol composition and is to be administered as a daily dose in tablets, preferably comprising 3mg drosiperone and 0.02 mg ethinyl estradiol of the active ingredients, respectively.

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The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and
(b) a hormonal substance, preferably chosen from the group consisting of a testosterone transdermal spray, a testosterone gel, a female testosterone patch, synthetic conjugated estrogen A, methyltestosterone, a estrogens/methyltestosterone and a drosiperone/ethinyl estradiol composition, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of premenstrual syndrome and sexual and gender identity disorders.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said hormonal substance is synthetic conjugated estrogen A, preferably provided in a unitary dose of between 0.075 and 0.6 mg of the active ingredient.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said hormonal substance is a drosiperone/ethinyl estradiol composition, preferably provided in tablets comprising a unitary dose of 3mg drosiperone and 0.02 mg ethinyl estradiol of the active ingredients, respedively.

44: combination therapy with a compound which increases brain concentrations of 5-HT

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
5 with a compound which increases brain concentrations of 5-HT (serotonin), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-
10 related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
15 emotion dysregulation of a non cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders,
20 personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound
25 which increases brain concentrations of 5-HT (serotonin), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
30 emotion dysregulation of pain, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases brain concentrations of 5-HT (serotonin) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said
35 compound which increases brain concentrations of 5-HT (serotonin), further characterized

in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described
5 above, wherein said compound which increases brain concentrations of 5-HT (serotonin) is chosen from the group consisting of triptosine, SP 186, PMD 145 and KW 6055, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
10 and (b) a compound which increases brain concentrations of 5-HT (serotonin), preferably chosen from the group consisting of triptosine, SP 186, PMD 145 and KW 6055, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from
15 the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems
20 related to abuse or neglect and pain disorders.

45: combination therapy with a compound which increases insulin sensitivity

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
25 with a compound which increases insulin sensitivity, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic
30 disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting

dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which increases insulin sensitivity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which increases insulin sensitivity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which increases insulin sensitivity is rosiglitazone maleate, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which increases insulin sensitivity, preferably rosiglitazone maleate or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

46: combination therapy with a compound inhibiting the mixed lineage kinase family

- 30 The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which is an inhibitor of the mixed lineage kinase family is Parkinson Disease.
- 35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is an inhibitor of the mixed lineage kinase family to augment the therapeutic effect or to provide a faster onset of the 5 therapeutic effect of said compound which is an inhibitor of the mixed lineage kinase family, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, 10 wherein said compound which is an inhibitor of the mixed lineage kinase family is CEP-1347 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, 15 and (b) a compound which is an inhibitor of the mixed lineage kinase family, preferably CEP-1347 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

20 **47: combination therapy with an interleukin-1 beta converting enzyme inhibitor compound**
The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an interleukin-1 beta converting enzyme inhibitor compound, is a pain disorder.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an interleukin-1 beta converting enzyme inhibitor 30 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said interleukin-1 beta converting enzyme inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said interleukin-1 beta converting enzyme inhibitor is pralnacasan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an interleukin-1 beta converting enzyme inhibitor, preferably pralnacasan or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a pain disorder.,

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48: combination therapy with a levodopa/decarboxylase inhibitor compound

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a levodopa/decarboxylase inhibitor compound, is Parkinson Disease.

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- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a levodopa/decarboxylase inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said levodopa/decarboxylase inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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- According to a preferred embodiment, the invention relates to the use as described above, wherein said levodopa/decarboxylase inhibitor compound is chosen from the group consisting of levodopa / carbidopa, levodopa / benserazide, etilevodopa / carbidopa or etilevodopa / benserazide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, levodopa / carbidopa is to be administered in a dialy dose between 250 to 600 mg / 25 to 150 mg of the active ingredients. Preferably, levodopa / benserazide is to be administered in a dialy dose between 100 to 600 mg / 25 to 150 mg of the active ingredients.

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- 30 According to a further preferred embodiment, the invention relates to the use as described above, wherein said levodopa/decarboxylase inhibitor compound is (eti)levodopa /

- carbidopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, said levodopa/decarboxylase inhibitor
- 5 compound is levodopa/carbidopa and is to be administered in a dose ranging between 2000 mg/ 50 mg and 100 mg/ 10 mg of the active ingredients. Preferably said entacapone is to be administered in a dose ranging between 1000 mg/ 50 mg, more preferably between 500 mg/ 100 mg, and most preferably 200 mg of the active ingredients per day.
- 10 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a levodopa/decarboxylase inhibitor compound, preferably levodopa / carbidopa, levodopa / benserazide, etilevodopa / carbidopa or etilevodopa / benserazide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the
- 15 underlying emotion dysregulation of Parkinson Disease. The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a levodopa/decarboxylase inhibitor compound, preferably is (eti)levodopa/carbidopa, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof in combination with entacapone, which is an inhibitor of catechol-O-methyltransferase (COMT), or a pro-drug
- 20 or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.
- The invention also relates to a pharmaceutical composition as described above wherein
- 25 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboxylase inhibitor compound is levodopa / carbidopa, preferably provided in a unitary dose of between 250 to 600 mg and 25 to 150 mg of the active ingredients.
- 30 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboxylase inhibitor compound is levodopa / benserazide, preferably provided in a unitary dose of between 100 to 600 mg and 25 to 150 mg of the active ingredients.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said levodopa/decarboxylase inhibitor compound is levodopa / carbidopa or etilevodopa / carbidopa in combination with entacapone, of which the latter is preferably 5 provided in a unitary dose of between 500 mg and 100 mg of the active ingredient.

49: combination therapy with a lipid-DNA complex

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy 10 with a lipid-DNA complex, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said 15 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of lipid-DNA complex to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said lipid-DNA complex, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20 According to a preferred embodiment, the invention relates to the use as described above, wherein said lipid-DNA complex is GR213487B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

25 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a lipid-DNA complex, preferably GR213487B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

30 **50: combination therapy with a monoamine oxidase (MAO) reuptake inhibitor**

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase (MAO) reuptake inhibitor, are chosen from the group of 35 diseases or disorders consisting of substance related disorders and attention-deficit disorders (ADHD).

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of non-cognitive mental disease or disorder which are substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention-deficit disorders (ADHD), characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase (MAO) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase (MAO) reuptake inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase (MAO) reuptake inhibitor compound is NS 2359 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase (MAO) reuptake inhibitor, preferably NS 2359 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of substance related disorders and attention-deficit disorders (ADHD).

51: combination therapy with a MAO-A and a MAO-B reuptake inhibitor

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake 5 inhibitor, wherein said disorders are attention-deficit disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of attention-deficit disorders, characterized in that pipamperon or 10 said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound, further 15 characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake inhibitor compound is SPD473 or a pro-drug or an active metabolite thereof, 20 or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase A (MAO-A) and a monoamine oxidase B (MAO-B) reuptake 25 inhibitor, preferably SPD473 or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of attention-deficit disorders.

52: combination therapy with a monoamine oxidase B (MAO-B) inhibitor

The mental disorders which can be treated using compounds having a high selective 30 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase B (MAO-B) inhibitor, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, 35 dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit

disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) inhibitor compound, further characterized in that

pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said monoamine oxidase B (MAO-B) inhibitor compound is chosen from the group consisting of selegiline, rasagiline (TVP-1012) and EmSam (transdermal selegiline), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said monoamine oxidase B (MAO-B) inhibitor is selegiline and is to be administered in a daily dose ranging between 5 and 60 mg or possibly between 5 and 10 mg of the active ingredient. In a further preferred embodiment, selegiline is to be administered in a transdermal application in a daily dose ranging between 5 and 60 mg of the active ingredient. In another preferred embodiment, selegiline is to be administered orally in a daily dose ranging between 5 and 10 mg of the active ingredient. More preferably, said monoamine oxidase B (MAO-B) inhibitor is rasagiline (TVP-1012) and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase B (MAO-B) inhibitor, preferably chosen from the group consisting of selegiline, rasagiline (TVP-1012) and EmSam (transdermal selegiline), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorder and Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said monoamine oxidase B (MAO-B) inhibitor is selegiline, preferably provided in a unitary dose of between 5 and 10 mg or between 5 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said monoamine oxidase B (MAO-B) inhibitor is rasagiline (TVP-1012), preferably provided in a unitary dose of between 1 and 2 mg of the active ingredient.

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53: combination therapy with a monoamine oxidase B (MAO-B) reuptake inhibitor

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a monoamine oxidase B (MAO-B) reuptake inhibitor, is Parkinson Disease.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a monoamine oxidase B (MAO-B) reuptake inhibitor to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said monoamine oxidase B (MAO-B) reuptake inhibitor, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the use as described above wherein said monoamine oxidase B (MAO-B) reuptake inhibitor is safinamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

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25 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a monoamine oxidase B (MAO-B) reuptake inhibitor, preferably safinamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

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54: combination therapy with a melanocortin-4 (MC4) receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a melanocortin-4 (MC4) receptor antagonist compound, are chosen from the group of 35 diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious

disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanocortin-4 (MC4) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanocortin-4 (MC4) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanocortin-4 (MC4) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanocortin-4 (MC4) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the uses as described above, wherein said melanocortin-4 (MC4) receptor antagonist compound is MCL0129, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

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35 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melanocortin-4 (MC4) receptor antagonist compound, preferably MCL0129 or a

pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

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55: combination therapy with a MCH receptor antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a melanin concentrating hormone (MCH) receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanin concentrating hormone (MCH) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanin concentrating hormone (MCH) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said 5 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melanin concentrating hormone (MCH) receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melanin concentrating hormone (MCH) receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a 10 daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melanin concentrating hormone (MCH) receptor antagonist compound is SNAP-7941 or a pro-drug or an active metabolite thereof, or a 15 pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melanin concentrating hormone (MCH) receptor antagonist compound, preferably SNAP-7941 or a pro-drug or an active metabolite thereof, or a pharmaceutically 20 acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity 25 disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

56: combination therapy with a melatonin receptor (MT) agonist compound

30 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a melatonin receptor (MT) agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious 35 disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality

disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a melatonin receptor (MT) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said melatonin receptor (MT) agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said melatonin receptor (MT) agonist compound is chosen from the group consisting of ramelteon and agomelatine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said melatonin receptor (MT) agonist compound is agomelatine and is to be administered in a daily dose ranging between 25 and 50 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a melatonin receptor (MT) agonist compound, preferably ramelteon or agomelatine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said melatonin receptor (MT) agonist compound is agomelatine, preferably provided in a unitary dose of between 25 and 50 mg of the active ingredient.

57: combination therapy with a metabotropic glutamate receptor (MgluR) agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a metabotropic glutamate receptor (MgluR) agonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a metabotropic glutamate receptor (MgluR) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said metabotropic glutamate receptor (MgluR) agonist compound, further characterized in that pipamperon is to be
5 administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
10 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a metabotropic glutamate receptor (MgluR) agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said metabotropic glutamate receptor (MgluR) agonist compound, further
15 characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said metabotropic glutamate receptor (MgluR) agonist compound is
20 PRE703 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a metabotropic glutamate receptor (MgluR) agonist, preferably PRE703 or a pro-
25 drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse
30 control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

58: combination therapy with a compound mimicking the effect of nerve growth factor (NGF)

35 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy

- with a compound which mimics the effect of nerve growth factor (NGF), are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,
5 dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head
15 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered
20 simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
25 ingredient.
- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said
30 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which mimics the effect of nerve growth factor (NGF) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which mimics the effect of nerve growth factor (NGF), further characterized in that pipamperon is to be administered to a patient in a daily dose
35 ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which mimics the effect of nerve growth factor (NGF) is xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said compound which mimics the effect of nerve growth
5 factor (NGF) is xaliproden and is to be administered in a daily dose ranging between 1 and 2 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which mimics the effect of nerve growth factor (NGF), preferably
10 xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head
15 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.
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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound which mimics the effect of nerve growth factor (NGF) is xaliproden, preferably provided in a unitary dose of between 1 and 2 mg of the active
25 ingredient.

59: combination therapy with a muscarinic receptor partial agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
30 with a muscarinic receptor partial agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic
35 disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of 5 diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic 10 disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a muscarinic receptor partial agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said muscarinic receptor partial agonist compound, further 15 characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said muscarinic receptor partial agonist compound is sevimeline or a pro-drug or 20 an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a muscarinic receptor partial agonist compound, preferably sevimeline or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a 25 combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick 30 Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

60: combination therapy with a selective nor-adrenaline re-uptake inhibitor (NARI) compound

- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy
- 5 with a selective nor-adrenaline re-uptake inhibitor (NARI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders,
- 15 adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline re-uptake inhibitor (NARI) compound to augment the therapeutic
- 20 effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline re-uptake inhibitor (NARI)
- 30 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline re-uptake inhibitor (NARI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 35 According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is

chosen from the group consisting of reboxetine, atomoxetine hydrochloride, A 75200, 155U88, (S)-A 75200, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective nor-adrenaline re-uptake inhibitor (NARI) compound is reboxetine and is to be administered in a daily dose ranging between 5 8 and 12 mg of the active ingredient. More preferably, said selective nor-adrenaline re-uptake inhibitor (NARI) compound is atomoxetine hydrochloride and is to be administered in a daily dose ranging between 40 and 100 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, 10 and (b) a selective nor-adrenaline re-uptake inhibitor (NARI) compound, preferably chosen from the group consisting of reboxetine, atomoxetine hydrochloride, A 75200, 155U88, (S)-A 75200, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or 15 disorder which is chosen from the group consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

20 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is reboxetine, preferably provided in a unitary dose of between 8 and 12 mg of the active ingredient.

25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline re-uptake inhibitor (NARI) compound is atomoxetine hydrochloride, preferably provided in a unitary dose of between 40 and 100 30 mg of the active ingredient.

61: combination therapy with a NaSSA compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy 35 with a noradrenergic-specific serotonergic antidepressant (NaSSA) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety

disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a noradrenergic/specific serotonergic antidepressant (NaSSA) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said noradrenergic/specific serotonergic antidepressant (NaSSA) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said noradrenergic/specific serotonergic antidepressant (NaSSA) compound is ORG 4420 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a noradrenergic/specific serotonergic antidepressant (NaSSA) compound, preferably ORG 4420 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

62: combination therapy with a selective NDRI compound

15 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, 20 antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic 25 disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the 30 group of diseases and disorders consisting of mood disorders, anxiety disorders, adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is 35 administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment

the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate 10 from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced 20 persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized 25 in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, further characterized 30 in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) 35 compound is GW353162 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective nor-adrenaline

and dopamine re-uptake inhibitor (NDRI) compound is GW353162 and is to be administered in a daily dose ranging between 20 and 60 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
5 and (b) a selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound, preferably GW353162 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders,
10 adjustment disorders, attention-deficit disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick
15 Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The invention also relates to a pharmaceutical composition as described above wherein
20 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective nor-adrenaline and dopamine re-uptake inhibitor (NDRI) compound is GW353162, preferably provided in a unitary dose of between 20 and 60 mg of the active ingredient.

25 **63: combination therapy with a compound which is a neuroimmunophilin ligand**

The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which is a neuroimmunophilin ligand, is Parkinson Disease.

30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a neuroimmunophilin ligand to
35 augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a neuroimmunophilin ligand, further characterized in that pipamperon

is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient

According to a preferred embodiment, the invention relates to the use as described above
5 wherein said a compound which is a neuroimmunophilin ligand is GPI 1485 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said a compound which is a neuroimmunophilin ligand is GPI 1485 and is to be administered in a daily dose ranging between 200 and 1000 mg of the active ingredient.

10

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a neuroimmunophilin ligand, preferably GPI 1485 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the
15 underlying emotion dysregulation of Parkinson Disease.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said a compound which is a neuroimmunophilin ligand is GPI 1485, 20 preferably provided in a unitary dose of between 200 and 1000 mg of the active ingredient.

64: combination therapy with a neuromodulator compound

The mental disorder which can be treated using compounds having a high selective
25 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neuromodulator compound, is Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
30 emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neuromodulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neuromodulator compound, further characterized in that pipamperon is to be administered
35 to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said neuromodulator compound is adenosine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neuromodulator compound, preferably adenosine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of Parkinson Disease.

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65: combination therapy with a neurotensin receptor antagonist compound

- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neurotensin receptor antagonist compound, are chosen from the group of diseases 15 or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, 20 antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 25 emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related 30 disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate 35 from or prior to the administration of a neurotensin receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurotensin receptor antagonist compound, further characterized in that pipamperon is to

be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neuropeptide Y receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neuropeptide Y receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neuropeptide Y receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neuropeptide Y receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said neuropeptide Y receptor antagonist compound is SR 48692 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neuropeptide Y receptor antagonist compound is SR 48692 and is to be administered in a daily dose ranging between 90 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neuropeptide Y receptor antagonist compound, preferably SR 48692 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep

disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said neurotensin receptor antagonist compound is SR 48692, preferably provided in a unitary dose of between 90 and 300 mg of the active ingredient.

66: combination therapy with nerve growth factor (NGF) gene therapy

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with nerve growth factor (NGF) gene therapy, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nerve growth factor (NGF) gene therapy, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to nerve growth factor (NGF) gene therapy, to augment the therapeutic effect or to provide a faster onset of nerve growth factor (NGF) gene therapy, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound useful in nerve growth factor (NGF) gene therapy, preferably xaliproden or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

It should be understood that "nerve growth factor gene therapy" is well known in the art, and the compounds, for instance nucleic acids used in nerve growth factor gene therapy are well described (see e.g. Tuszyński *et al.*, (2002) Journal of Molecular Neuroscience Volume 19, Issue 1-2, pps. 207-208).

67: combination therapy with a nicotinic acetylcholine receptor antagonist compound
The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a nicotinic acetylcholine receptor antagonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse

control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, 10 bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic acetylcholine receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic acetylcholine receptor 15 antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic acetylcholine receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said nicotinic acetylcholine receptor antagonist compound, further characterized 25 in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said nicotinic acetylcholine receptor antagonist compound is SEP174559 30 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a nicotinic acetylcholine receptor antagonist compound, preferably SEP174559 or 35 a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the

underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of anxiety disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, 5 occupational problem, problems related to abuse or neglect and pain disorders.

68: combination therapy with a nicotinic receptor agonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy 10 with a nicotinic receptor agonist compound, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general 15 medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 20 emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic 25 disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a nicotinic receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the 30 therapeutic effect of said nicotinic receptor agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above 35 wherein said nicotinic receptor agonist compound is ABT-089, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said

nicotinic receptor agonist compound is ABT-089 and is to be administered in a daily dose ranging between 4 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
5 and (b) a nicotinic receptor agonist compound, preferably ABT-089 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular
10 dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

15 The invention also relates to a pharmaceutical composition as described above, wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said nicotinic receptor agonist compound is ABT-089, preferably provided in a unitary dose of between 4 and 40 mg of the active ingredient.

20 **69: combination therapy with a neurokinin 2 receptor (NK2) antagonist compound**
The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neurokinin 2 receptor (NK2) antagonist compound, are chosen from the group of
25 diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and
30 pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),

- factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt
5 thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
15 from or prior to the administration of a neurokinin 2 receptor (NK2) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 2 receptor (NK2) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 20 According to a preferred embodiment, the invention relates to the uses as described above, wherein said neurokinin 2 receptor (NK2) antagonist compound is saredutant or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said neurokinin 2 receptor (NK2) antagonist compound is saredutant and
25 is to be administered in a daily dose ranging between 25 and 200 mg of the active ingredient.
- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a neurokinin 2 receptor (NK2) antagonist compound, preferably saredutant or a
30 pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders,
35 dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders,

bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein
5 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said neurokinin 2 receptor (NK2) antagonist compound is saredutant, preferably provided in a unitary dose of between 25 and 200 mg of the active ingredient.

70: combination therapy with a neurokinin 3 receptor (NK3) antagonist compound

- 10 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a neurokinin 3 receptor (NK3) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders,
15 dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.
- 20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders,
25 psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem
30 and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that
35 pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said 5 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 10 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, 15 characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a neurokinin 3 receptor (NK3) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said neurokinin 3 receptor (NK3) antagonist compound, further characterized in that pipamperon is to be administered to a 20 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said neurokinin 3 receptor (NK3) antagonist compound is talnetant or osanetant, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable 25 salt thereof. More preferably, said neurokinin 3 receptor (NK3) antagonist compound is talnetant and is to be administered in a daily dose ranging between 1.5 and 12 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, 30 and (b) a neurokinin 3 receptor (NK3) antagonist compound, preferably talnetant or osanetant, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, 35 somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive

development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said neurokinin 3 receptor (NK3) antagonist compound is talnetant, preferably provided in a unitary dose of between 1.5 and 12 mg of the active ingredient

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71: combination therapy with an N-Methyl-D-aspartate (NMDA) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an N-Methyl-D-aspartate (NMDA) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-

aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an N-Methyl-D-aspartate (NMDA) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said N-Methyl-D-aspartate (NMDA) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said N-Methyl-D-aspartate (NMDA) antagonist compound is chosen from the group consisting of SEP174559, memantine, delucemine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said N-

Methyl-D-aspartate (NMDA) antagonist compound is memantine and is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

- The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
5 and (b) an N-Methyl-D-aspartate (NMDA) antagonist compound, preferably chosen from the group consisting of SEP174559, memantine, delucemine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group
10 consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.
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- The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said N-Methyl-D-aspartate (NMDA) antagonist compound is memantine, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient.
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- 72: combination therapy with a non-steroidal anti-inflammatory drug
The mental disorder which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a non-steroidal anti-inflammatory drug, is a pain disorder or Alzheimer Disease.
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- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a pain disorder, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
35 from or prior to the administration of a non-steroidal anti-inflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-

steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive disease, such as Alzheimer Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a non-steroidal anti-
- 10 inflammatory drug to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said a non-steroidal anti-inflammatory drug, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 15 According to a preferred embodiment, the invention relates to the uses as described above, wherein said a non-steroidal anti-inflammatory drug is chosen from the group consisting of piroxicam, MX-1094, meloxicam and flurizan (pure R-enantiomer form of flurbiprofen), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- 20 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a non-steroidal anti-inflammatory drug, preferably chosen from the group consisting of piroxicam, MX-1094, meloxicam and flurizan (pure R-enantiomer form of flurbiprofen), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a pain disorder or Alzheimer Disease.

73: combination therapy with an opioid receptor antagonist compound

- 30 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an opioid receptor antagonist compound are substance related disorders.

It will be appreciated that the terms "opoid" and "opioid" may be used interchangeably.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of substance related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with,
- 5 separate from or prior to the administration of a opioid receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said opioid receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 According to a preferred embodiment, the invention relates to the use as described above, wherein said opioid receptor antagonist compound is naltrexone, preferably as a depot formulation, more preferably in the form of microcapsules, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, said
- 15 naltrexone is to be administered in the form of a depot, preferably a depot of microcapsules comprising a daily dose of between 192 and 384 mg.
- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an opioid receptor antagonist, preferably naltrexone, or a pro-drug or an active
- 20 metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of substance related disorders.
- The invention also relates to a pharmaceutical composition as described above wherein
- 25 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said opioid receptor antagonist compound is naltrexone, preferably provided in a unitary dose of between 192 and 384 mg of the active ingredient.
- 74: combination therapy with an opioid agonist compound
- 30 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with an opioid agonist compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders,
- 35 dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment

disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of an opioid agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said opioid agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said opioid agonist compound is chosen from the group consisting of siramesine, E-5842 and cyclazocine, preferably siramesine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) an opioid agonist compound, preferably chosen from the group consisting of siramesine, E-5842 and cyclazocine, preferably siramesine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

75: combination therapy with a phosphodiesterase-4 (PDE4) inhibitor compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a phosphodiesterase-4 (PDE4) inhibitor compound, are chosen from the group of

5 diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease,

10 substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive

15 disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the

20 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that

25 pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging

30 between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound d

to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phosphodiesterase-4 (PDE4) inhibitor compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phosphodiesterase-4 (PDE4) inhibitor compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said phosphodiesterase-4 (PDE4) inhibitor compound is chosen from the group consisting of ND1251 and MEM 1917 (R1497), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a phosphodiesterase-4 (PDE4) inhibitor antagonist compound, preferably chosen from the group consisting of ND1251 and MEM 1917 (R1497), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to

abuse or neglect, pain disorders, Alzheimer Disease, substance-related persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic
5 disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

76: combination therapy with a peptidic compound

- The mental disorders which can be treated using compounds having a high selective
10 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a peptidic compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders,
15 impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to
20 Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.
- 25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
30 factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is
35 administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic effect or to provide a faster onset of the therapeutic

effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to augment the therapeutic
10 effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease,
20 dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a peptidic compound to
25 augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said peptidic compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

30 According to a preferred embodiment, the invention relates to the uses as described above, wherein said peptidic compound is chosen from the group consisting of secretin, PT-141, INN 00835 and beta sheet breaker peptide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said peptidic compound is secretin and is to be administered in a daily dose ranging between 0.2 and 0.4 mg/kg of the active ingredient. More preferably, said peptidic compound is INN 00835
35 and is to be administered in a daily dose ranging between 18 and 160 mg of the active ingredient.

- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a peptidic compound, preferably chosen from the group consisting of secretin, PT-141, INN 00835 and beta sheet breaker peptide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.
- 20 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said peptidic compound is secretin, preferably provided in a unitary dose of 0.2 and 0.4 mg/kg of the active ingredient.
- 25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said peptidic compound is INN 00835, preferably provided in a unitary dose of 18 and 160 mg of the active ingredient.
- 30 77: combination therapy with a phospholipase A2 inhibitor compound
The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a phospholipase A2 inhibitor compound which has caspase inhibitor activity, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual

and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, 10 psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders; bereavement, occupational problem and problems 15 related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity, 20 further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 25 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase 30 inhibitor activity, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 35 emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a phospholipase A2 inhibitor compound which has caspase inhibitor activity to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said phospholipase A2 inhibitor compound which has caspase inhibitor activity, further
5 characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said phospholipase A2 inhibitor compound which has caspase inhibitor
10 activity is chosen from the group consisting of LAX-101a, LAX-101b and LAX-101c, preferably LAX-101c, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
15 and (b) a phospholipase A2 inhibitor compound which has caspase inhibitor activity, preferably chosen from the group consisting of LAX-101a, LAX-101b and LAX-101c, more preferably LAX-101c, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or
20 disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related
25 disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

78: combination therapy with a compound which is a prodrug of uridine

The mental disorders which can be treated using compounds having a high selective
30 affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which is a prodrug of uridine, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment
35 disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the
5 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect,
10 characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a prodrug of uridine to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a prodrug of uridine, further characterized in that pipamperon is to be administered to a patient in a daily dose
15 ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
20 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a prodrug of uridine to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a prodrug of uridine, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active
25 ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which is a prodrug of uridine is RG2133 (triacetyluridine) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt
30 thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a prodrug of uridine, preferably RG2133 (triacetyluridine) or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof,
35 as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from

the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

79: combination therapy with prostaglandin E1 compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy 10 with prostaglandin E1 compound, are sexual and gender identity disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the 15 group of sexual and gender identity disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a prostaglandin E1 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said prostaglandin E1 compound, further characterized in that pipamperon is to be 20 administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said prostaglandin E1 is alprostadil or a pro-drug or an active metabolite thereof, 25 or a pharmaceutically acceptable salt thereof. More preferably, said prostaglandin E1 compound is alprostadil, preferably in the form of cream or gel, preferably a topical gel, and is to be administered in a daily dose ranging between 50 and 300 microgram per application of the active ingredient.

30 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a prostaglandin E1 compound, preferably alprostadil or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of 35 sexual and gender identity disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said prostaglandin E1 compound is alprostadil, preferably provided in the form of a cream or gel, preferably a topical gel, wherein a unitary dose comprises between 5 50 and 300 microgram of the active ingredient per application.

80: combination therapy with a compound protecting dopaminergic and cholinergic neurons

10 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which protects dopaminergic and cholinergic neurons, are chosen from the group of diseases or disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, 15 dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head 25 trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered 30 simultaneously with, separate from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active 35 ingredient.

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which protects dopaminergic and cholinergic neurons to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which protects dopaminergic and cholinergic neurons, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which protects dopaminergic and cholinergic neurons is SR 57667 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- 15 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which protects dopaminergic and cholinergic neurons, preferably SR 57667 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for
- 20 treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic
- 25 disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.
- 81: combination therapy with a psycho stimulant
- 30 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a psycho stimulant, are chosen from the group of diseases or disorders consisting of sleep disorders, attention-deficit disorders and substance-related disorders.
- 35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

- emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of sleep disorders, attention-deficit disorders and substance-related disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a psycho stimulant to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said psycho stimulant, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 According to a preferred embodiment, the invention relates to the uses as described above, wherein said psycho stimulant is chosen from the group consisting of SPD 503, r-modafinil and modafinil, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said psycho stimulant is SPE 503, more preferably said psycho stimulant is modafinil and is to be administered in a
- 15 daily dose ranging between 200 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a psycho stimulant, preferably chosen from the group consisting of SPD 503, r-modafinil and modafinil, more preferably said SPC 503 or modafinil or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of sleep disorders, attention-deficit disorders and substance-related disorders.

25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said psycho stimulant is modafinil, preferably provided in a unitary dose of between 200 and 600 mg of the active ingredient

30 82: combination therapy with a compound which is a Reversible Inhibitor of Mono-Amine oxydase A (RIMA)

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy 35 with a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety

disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is chosen from the group consisting of toloxatone, RS 8359, moclobemide, cimoxatone, caroxazone (F.I 6654) and beflroxatone, or a pro-drug or an active metabolite

thereof, or a pharmaceutically acceptable salt thereof. More preferably, said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is befloxatone and is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient.

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which is a reversible inhibitor of mono-amine oxydase A (RIMA), preferably chosen from the group consisting of toloxatone, RS 8359, moclobemide, cimoxatone, caroxazone (F.I 6654) and befloxatone, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for
10 simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, adjustment disorders, impulse control disorders, personality
15 disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein
20 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said compound which is a reversible inhibitor of mono-amine oxydase A (RIMA) is befloxatone, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

83: combination therapy with a compound which modulates SCT-11

- 25 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound which modulates SCT-11 (i.e. SCT-11 is a G protein-coupled receptor), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding
30 pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which modulates SCT-11 to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which modulates SCT-11, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound which modulates SCT-11 to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound which modulates SCT-11, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above, wherein said compound which modulates SCT-11 is SNEC-2 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound which modulates SCT-11, preferably SNEC-2 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders,

impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

84: combination therapy with a serotonin/dopamine antagonist compound (SDA)

- 5 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a serotonin/dopamine antagonist compound (SDA), are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, 10 dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.
- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, 20 psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem 25 and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to 30 be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

- 35 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate

from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a serotonin/dopamine antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said serotonin/dopamine antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said serotonin/dopamine antagonist compound is chosen from the group consisting of zotepine, ziprasidone, SM-13496, SL 91.0177, sertindole, S-18327, risperidone, quetiapine fumarate (preferably sustained release formulation), quetiapine fumarate (preferably granules), quetiapine, perospirone, paliperidone, olanzapine, oclaperidone, LU 31-131, iloperidone, clozapine, BSF-190555, bilonanserin, bifeprunox, asenapine and aripiprazole, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said serotonin/dopamine antagonist compound is chosen from the group consisting of SL 91.0177, sertindole, perospirone, paliperidone, bilonanserin, bifeprunox and asenapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said serotonin/dopamine antagonist compound is sertindole and is to be administered in a daily dose ranging between 12 and 24 mg of the active ingredient. More preferably, said serotonin/dopamine antagonist compound is paliperidone and is to be administered in a daily dose ranging between 3 and 15 mg of the active ingredient. More preferably, said serotonin/dopamine antagonist compound is asenapine and is to be administered in a daily dose ranging between 2.5 and 20 mg of the active ingredient.

35 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a serotonin/dopamine antagonist compound, preferably chosen from the group

consisting of SL 91.0177, sertindole, perospirone, paliperidone, bilonanserin, bifeprunox and asenapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is sertindole, preferably provided in a unitary dose of between 12 and 24 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is paliperidone, preferably provided in a unitary dose of between 3 and 15 mg of the active ingredient.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said serotonin/dopamine antagonist compound is asenapine, preferably provided in a unitary dose of between 2.5 and 20 mg of the active ingredient.

85: combination therapy with a selective SDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin and dopamine re-uptake inhibitor (SDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or

neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic
5 disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
10 emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour,
15 bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective
20 serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
25 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI)
30 compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
35 emotion dysregulation of a cognitive mental disease or disorder selected from the group

- of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and dopamine reuptake inhibitor (SDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and dopamine reuptake inhibitor (SDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 15 According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin and dopamine reuptake inhibitor (SDRI) compound is bazinaprine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.
- 20 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin and dopamine reuptake inhibitor (SDRI) compound, preferably bazinaprine or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.
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86: combination therapy with a second messenger beta agonist compound

- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a second messenger beta agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 15 20 25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a second messenger beta agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said second messenger beta agonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
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According to a preferred embodiment, the invention relates to the uses as described above, wherein said second messenger beta agonist compound is chosen from the group consisting of SR 57227, rolipram and eplivanserin, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said second messenger beta agonist compound is rolipram and is to be administered in a daily dose ranging between 1.5 and 3 mg of the active ingredient.

- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a second messenger beta agonist compound, preferably chosen from the group consisting of SR 57227, rolipram and eplivanserin or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 20 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said second messenger beta agonist compound is rolipram, preferably provided in a unitary dose of between 1.5 and 3 mg of the active ingredient.

25 87: combination therapy with a secretin pancreatic hormone

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a secretin pancreatic hormone, are chosen from the group of diseases or disorders consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, psychotic disorders,
5 somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem and problems
10 related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging
15 between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
20 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is
30 administered simultaneously with, separate from or prior to the administration of a secretin pancreatic hormone to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said secretin pancreatic hormone, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said secretin pancreatic hormone is RG1068 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- 5 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a secretin pancreatic hormone, preferably RG1068, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group
10 consisting of anxiety disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement,
15 occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

88: combination therapy with a sigma receptor agonist compound

- The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a sigma receptor agonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment
20 disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
25

- The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep
30 disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem and problems related to abuse
35

or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor agonist compound, further 5 characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying 10 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor agonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor agonist compound, further characterized in that pipamperon is to be administered 15 to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said sigma receptor agonist compound is VPI-013 (also known as OPC-14523) or PRX-00023, preferably VPI-013 (also known as OPC-14523), or a pro-drug or 20 an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sigma receptor agonist compound, preferably VPI-013 (also known as OPC-14523) or PRX-00023, preferably VPI-013 (also known as OPC-14523), or a pro-drug or 25 an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative 30 disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

89: combination therapy with a sigma receptor antagonist compound

35 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy

- with a sigma receptor antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders 15 (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically 20 acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate 30 from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is 5 administered simultaneously with, separate from or prior to the administration of a sigma receptor antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sigma receptor antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the uses as described above, wherein said sigma receptor antagonist compound is chosen from the group consisting of SR 31742 and EMD 68843, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said sigma receptor 15 antagonist compound is EMD 68843 and is to be administered in a daily dose ranging between 5 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sigma receptor antagonist compound, preferably chosen from the group 20 consisting of SR 31742 and EMD 68843, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform 25 disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect, pain disorders and delirium.

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The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said sigma receptor antagonist compound is EMD 68843, preferably provided in a unitary dose of between 5 and 40 mg of the active ingredient

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90: combination therapy with a selective SNDRI compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

- emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a
- 5 faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 10 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to
- 15 head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered
- 20 simultaneously with, separate from or prior to the administration of a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging
- 25 between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI) compound is selected from the group consisting of NS 2330; McN 5652; DOV

30 216,303 and DOV 21,947; more preferably NS 2330 or DOV 216,303; or a pro-drug or an active metabolite thereof; or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin, nor-adrenaline and dopamine re-uptake inhibitor (SNDRI)

35 compound, preferably selected from the group consisting of NS 2330; McN 5652; DOV 216,303 and DOV 21,947, more preferably NS 2330 or DOV 216,303, or a pro-drug or an

- active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome,
5 somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia,
10 dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders.
- 15 **91: combination therapy with a selective SNRI compound**
The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, are
20 chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
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The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the
30 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related
35 to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the

administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose
5 ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said
10 pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, further characterized in that pipamperon is to be administered to a
15 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is selected from the group consisting of venlafaxine, tomoxetine, tandamine,
20 talsupram, talopram, nefazodone, milnacipran, LY 113.821, duloxetine, desvenlafaxine and amoxapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is chosen from the group consisting of venlafaxine, tomoxetine, milnacipran, duloxetine and desvenlafaxine, or a pro-drug or an active
25 metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is venlafaxine and is to be administered in a daily dose ranging between 75 and 300 mg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is tomoxetine and is to be administered in a daily dose ranging
30 between 0.475 and 3.8 mg/kg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is milnacipran and is to be administered in a daily dose ranging between 50 and 200 mg of the active ingredient. More preferably, said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is duloxetine and is to be administered in a daily dose ranging between 40 and
35 60 mg of the active ingredient.

- The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound, preferably selected from the group consisting of venlafaxine, tomoxetine, tandamine, talsupram, talopram, nefazodone, milnacipran, LY 113.821, duloxetine, desvenlafaxine and amoxapine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
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- The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is venlafaxine, preferably provided in a unitary dose of between 75 and 300 mg of the active ingredient.
- The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is tomoxetine, preferably provided in a unitary dose of between 0.475 and 3.8 mg/kg of the active ingredient.
- The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI) compound is milnacipran, preferably provided in a unitary dose of between 50 and 200 mg of the active ingredient.
- The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin and nor-adrenaline re-uptake inhibitor (SNRI)

compound is duloxetine, preferably provided in a unitary dose of between 40 and 60 mg of the active ingredient.

92: combination therapy with a selective serotonin re-uptake inhibitor (SSRI) compound

- 5 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a selective serotonin re-uptake inhibitor (SSRI) compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
- 10 factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
- 20 factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, antisocial behaviour, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a
- 25 selective serotonin re-uptake inhibitor (SSRI) compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a selective serotonin re-uptake inhibitor (SSRI)
- 35 compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said selective serotonin re-uptake inhibitor (SSRI) compound, further

characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said selective serotonin re-uptake inhibitor (SSRI) compound is selected from the group consisting of YM 992, VPI-013 (also known as OPC-14523), sertraline, paroxetine, LY 214.281, LU AA 21-004, Lu 35-138, litoxetine, ifoxetine, fluvoxamine (controlled release formulation), fluvoxamine, fluoxetine, femoxetine, escitalopram, EMD 68843, cyanodothepine, citalopram, cericlamine and ademethionine (preferably s-adenosylmethionine), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Even more preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is chosen from the group consisting of litoxetine, fluvoxamine (controlled release formulation), citalopram and escitalopram, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is fluvoxamine (controlled release formulation) and is to be administered in a daily dose ranging between 100 and 300 mg of the active ingredient. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is escitalopram and is to be administered in a daily dose ranging between 10 and 20 mg of the active ingredient. More preferably, said selective serotonin re-uptake inhibitor (SSRI) compound is citalopram and is to be administered in a daily dose ranging between 10 and 40 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a selective serotonin re-uptake inhibitor (SSRI) compound, preferably selected from the group consisting of YM 992, VPI-013 (also known as OPC-14523), sertraline, paroxetine, LY 214.281, LU AA 21-004, Lu 35-138, litoxetine, ifoxetine, fluvoxamine (controlled release formulation), fluvoxamine, fluoxetine, femoxetine, escitalopram, EMD 68843, cyanodothepine, citalopram, venlafaxine, milnacipran, duloxetin, cericlamine and ademethionine (preferably s-adenosylmethionine), or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders,

personality disorders, antisocial behaviour, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein
5 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is fluvoxamine (controlled release formulation), preferably provided in a unitary dose of between between 100 and 300 mg of the active ingredient.

10 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is escitalopram, preferably provided in a unitary dose of between 10 and 20 mg of the active ingredient.

15 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said selective serotonin re-uptake inhibitor (SSRI) compound is citalopram, preferably provided in a unitary dose of between 10 and 40 mg of the active ingredient.

20 Citalopram or citalopram hydrobromide is a selective serotonin (5-hydroxytryptamine / 5-HT) re-uptake inhibitor (SSRI) and is the conventional name given for the compound of the formula (RS)-1-[3-(dimethylamino)propyl]-1-(p-fluorophenyl)-5-phthalancarbonitrile-hydro-bromide. According to an embodiment, a daily doses of active ingredient of SSRI, preferably citalopram, ranges between 10 and 40 mg per day. Preferably, daily doses of
25 active ingredient ranging between 20 and 30 mg per day are administered. More preferably, a daily dose of 10, 15, 20, 25, 30, 35 or 40 mg per day is administered.

Fluvoxamine or fluvoxamine maleate (luvox, fevarin) is a selective serotonin (5-HT) re-uptake inhibitor (SSRI) belonging to a new chemical series, the 2-aminoethyl oxime ethers of aralkylketones. It is chemically unrelated to other SSRIs and clomipramine. It is
30 chemically designated as 5-methoxy-4'-(trifluoromethyl) valerophenone (E)-O-(2-aminoethyl) oxime maleate (1:1).

According to an embodiment, a daily dose of active ingredient of fluvoxamine in a controlled release mode ranges between 100 and 300 mg per day. Preferably, daily doses of active ingredient ranging between 150 and 200 mg per day are administered in a

controlled release mode. More preferably, a daily dose of 100, 150, 200, 250 or 300 mg per day is administered by controlled release.

93: combination therapy with a substance P receptor (NK1) antagonist compound

- 5 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a substance P receptor (NK1) antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious
- 10 disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.
- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
- 20 factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of
- 25 a substance P receptor (NK1) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a substance P receptor (NK1) antagonist compound to augment the
- 35 therapeutic effect or to provide a faster onset of the therapeutic effect of said substance P receptor (NK1) antagonist compound, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described above, wherein said substance P receptor (NK1) antagonist compound is chosen from the group consisting of vestipitant, TAK-637, R673, GW823296, GW679769, GW597599, CP-122.721, aprepitant, 823296 and 679769, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said substance P receptor (NK1) antagonist compound is aprepitant and is to be administered in a daily dose ranging between 40 and 160 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a substance P receptor (NK1) antagonist compound, preferably chosen from the group consisting of vestipitant, TAK-637, R673, GW823296, GW679769, GW597599, CP-122.721, aprepitant, 823296 and 679769, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said substance P receptor (NK1) antagonist compound is aprepitant, preferably provided in a unitary dose of between 40 and 160 mg of the active ingredient.

94: combination therapy with a sulfonamide compound
The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a sulfonamide compound, are chosen from the group of diseases or disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment

disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain 5 disorders and delirium.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the 10 group of diseases and disorders consisting of mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, 15 antisocial behaviour, bereavement, occupational problem, identity problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further 20 characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further characterized in that pipamperon is to be administered to a patient in a daily dose 30 ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a cognitive mental disease or disorder which is delirium, 35 characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a

sulfonamide compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said sulfonamide compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

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According to a preferred embodiment, the invention relates to the uses as described above, wherein said sulfonamide compound is zonisamide or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said sulfonamide compound is zonisamide and is to be administered in a daily dose ranging

10 between 100 and 600 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a sulfonamide compound, preferably zonisamide, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting mood disorders, psychotic disorders, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, problems related to abuse or neglect, pain disorders and delirium.

25 The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said sulfonamide compound is zonisamide, preferably provided in a unitary dose of between 100 and 600 mg of the active ingredient.

30 95: combination therapy with a tachykinin antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a tachykinin antagonist compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment

disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
10 factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of
15 a tachykinin antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 20 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a tachykinin antagonist compound to augment the
25 therapeutic effect or to provide a faster onset of the therapeutic effect of said tachykinin antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

- 30 According to a preferred embodiment, the invention relates to the use as described above, wherein said tachykinin antagonist compound is SR 48968 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

- 35 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a tachykinin antagonist compound, preferably SR 48968 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying

emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, 5 impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

96: combination therapy with a compound selected from the group consisting of R228060

10 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, are chosen from the group of 15 diseases or disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, 20 substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem, problems related to abuse or neglect, pain disorders, delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia 25 due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

30 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders 35 (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders,

- pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient:
- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder and other cognitive disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is

administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound selected from the 5 group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson Disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-15 017.493, to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

20 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a compound selected from the group consisting of R228060 (YKP-10A), palanpanel, ORG 39479/PH80, ORG 34167, DP 543 and CJ-017.493, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined 25 preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, psychotic disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, 30 adjustment disorders, impulse control disorders, pervasive development disorders, attention-deficit disorders, disruptive behaviour disorders, substance-related disorders, personality disorders, psychological factors affecting medical conditions, malingering, antisocial behaviour, bereavement, occupational problem, identity problem, phase of life problem, academic problem, problems related to abuse or neglect, pain disorders, 35 delirium, Alzheimer Disease, substance-induced persisting dementia, vascular dementia, dementia due to HIV disease, dementia due to head trauma, dementia due to Parkinson

Disease, dementia due to Huntington Disease, dementia due to Pick Disease, dementia due to Creutzfeldt-Jacob Disease, amnestic disorders due to a general medical condition, substance-induced persisting amnestic disorder, mild cognitive impairment disorder, other cognitive disorders and Parkinson Disease.

5

97: combination therapy with a vasopressin 1B receptor (V1B) antagonist compound

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a vasopressin 1B receptor (V1B) antagonist compound, are chosen from the group of 10 diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and 15 pain disorders.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the 20 group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse 25 or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a vasopressin 1B receptor (V1B) antagonist compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vasopressin 1B receptor (V1B) antagonist compound, further characterized in that pipamperon is to be administered to a 30 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a vasopressin 1B receptor (V1B) antagonist 35

compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said vasopressin 1B receptor (V1B) antagonist compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

5

According to a preferred embodiment, the invention relates to the uses as described above, wherein said vasopressin 1B receptor (V1B) antagonist compound is SSR149415 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

10

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a vasopressin 1B receptor (V1B) antagonist compound, preferably SSR149415 or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

98: combination therapy with a voltage-gated calcium channel $\alpha(2)\delta$ subunit modulator compound

25 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a voltage-gated calcium channel alpha(2)delta subunit modulator compound, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

35 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying

- emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a voltage-gated calcium channel alpha(2)delta subunit modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said voltage-gated calcium channel alpha(2)delta subunit modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 15 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a voltage-gated calcium channel alpha(2)delta subunit modulator compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said voltage-gated calcium channel alpha(2)delta subunit modulator compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.
- 20
- 25 According to a preferred embodiment, the invention relates to the uses as described above, wherein said voltage-gated calcium channel alpha(2)delta subunit modulator compound is pregabalin or PD-200,390; or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. More preferably, said voltage-gated calcium channel alpha(2)delta subunit modulator compound is pregabalin, and is to be administered in a daily dose ranging between 50 and 600 mg of the active ingredient.
- 30
- 35 The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) a voltage-gated calcium channel alpha(2)delta subunit modulator compound, preferably pregabalin or PD-200,390; or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental

disease or disorder which is chosen from the group consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, substance-related disorders, personality disorders, bereavement, occupational problem, problems related to abuse or neglect and pain disorders.

The invention also relates to a pharmaceutical composition as described above wherein pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient 10 and wherein said voltage-gated calcium channel alpha(2)delta subunit modulator compound is pregabalin, preferably provided in a unitary dose of between 50 and 600 mg of the active ingredient.

99: combination therapy with a vomeropherin compound

15 The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a vomeropherin compound, are chosen from the group of diseases or disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual 20 and gender identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

25 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender identity disorders, sleep disorders, 30 adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of vomeropherin compound to augment the therapeutic effect or to provide a faster onset of the therapeutic 35 effect of said vomeropherin compound, further characterized in that pipamperon is to be

administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the use as described above,
5 wherein said vomeropherin compound is PH94B or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon, and (b) vomeropherin compound, preferably PH94B or a pro-drug or an active metabolite
10 thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder which is chosen from the group consisting of anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, sexual and gender
15 identity disorders, sleep disorders, adjustment disorders, impulse control disorders, personality disorders, bereavement, occupational problem and problems related to abuse or neglect.

Also, the invention relates in particular to the use as described before, wherein said second compound is chosen from the group consisting of fluvoxamine controlled release,
20 phenserine tartrate, atomoxetine hydrochloride, bupropion (controlled-release formulation), ropinirole HCL (controlled-release formulation), INN 00835, galantamine (extended release formulation), paliperidone, tomoxytine, aprepitant, rivastigmine tartrate, ORG 34517/34850, sunepitron, sumanirole, milnacipran, idazoxan, xaliproden, SR 58611, beflroxatone, litoxetine, tianeptine, agomelatine, SPD 503, flesinoxan, bifeprunox,
25 ramelteon, etilevodopa, rasagiline (TVP-1012) and desvenlafaxine.

Also, the invention relates in particular to the use as described before, wherein said second compound is chosen from the group consisting of galantamine (extended release formulation), R121919, risperidone, paliperidone and R228060 (YKP-10A).

30 100: combination therapy with a dopamine releaser

The mental disorders which can be treated using compounds having a high selective affinity for the 5-HT2A and D4 receptor, for instance pipamperon, in a combination therapy with a dopamine releaser, are chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders, premenstrual syndrome,

somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

- 5 The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of a non-cognitive mental disease or disorder selected from the group of diseases and disorders consisting mood disorders, anxiety disorders, eating disorders, premenstrual syndrome, somatoform disorders (excluding pain disorders),
10 factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders and problems related to abuse or neglect, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine releaser compound to augment the
15 therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying
20 emotion dysregulation of pain disorders, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate from or prior to the administration of a dopamine releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine releaser compound, further characterized in that pipamperon is to be administered to a
25 patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

The present invention thus relates to the use of pipamperon or a pharmaceutically acceptable salt thereof for the preparation of a medicament for treating the underlying emotion dysregulation of Parkinson disease, characterized in that pipamperon or said pharmaceutically acceptable salt thereof is administered simultaneously with, separate
30 from or prior to the administration of a dopamine releaser compound to augment the therapeutic effect or to provide a faster onset of the therapeutic effect of said dopamine releaser compound, further characterized in that pipamperon is to be administered to a patient in a daily dose ranging between 5 and 15 mg of the active ingredient.

According to a preferred embodiment, the invention relates to the uses as described
35 above, wherein said dopamine (receptor) agonist compound is amantadine, or a pro-drug

or an active metabolite thereof, or a pharmaceutically acceptable salt thereof. Preferably, amantadine is to be administered in a daily dose of between 100 and 300 mg of the active ingredient.

The invention also relates to a pharmaceutical composition comprising (a) pipamperon,
5 and (b) a dopamine (receptor) agonist, preferably amantadine, or a pro-drug or an active metabolite thereof, or a pharmaceutically acceptable salt thereof, as a combined preparation for simultaneous, separate or sequential use for treating the underlying emotion dysregulation of a mental disease or disorder which is chosen from the group of diseases or disorders consisting of mood disorders, anxiety disorders, eating disorders,
10 premenstrual syndrome, somatoform disorders (excluding pain disorders), factitious disorders, dissociative disorders, adjustment disorders, impulse control disorders, attention-deficit disorders, substance-related disorders, personality disorders, problems related to abuse or neglect, pain disorders and Parkinson disease.

The invention also relates to a pharmaceutical composition as described above wherein
15 pipamperon is provided in a unitary dose of between 5 and 15 mg of the active ingredient and wherein said dopamine (receptor) agonist is amantadine, preferably provided in a unitary dose of between 100 and 300 mg of the active ingredient.

From the above it will be apparent that the numbering of the grouping according to the
20 action on the pathway or system corresponds to the numbering of the columns in Table 5 and the numbering of the pharmacological profile in Table 6.

The disclosure of all patents, publications (including published patent publications), and database accession numbers and depository accession numbers referenced in this specification are specifically incorporated herein by reference in their entirety to the same
25 extent as if each such individual patent, publication, and database accession number, and depository accession number were specifically and individually indicated to be incorporated by reference.

The invention, now being generally described, will be more readily understood by reference to the following tables and examples, which are included merely for purposes of
30 illustration of certain aspects and embodiments of the present invention and are not intended to limit the invention.

Short description of the Tables and Figures

Table 1: In Table 1, the pKi values of test compounds are given for each of the dopamine receptors, 5HT receptors, adrenergic receptors and the histamine1 receptor.

5

Table 2: Set-up of a clinical trial comprising for treatment groups.

Table 3: Overview of a placebo, active and period controlled clinical trial in a fore-going pipamperon - citalopram treatment in Major Depressive Disorder.

10

Table 4: POC process for major depressive disorder.

Table 5: Summary of diseases and disorders relative to known psycho-tropics.

15 **Table 6:** Overview of Pharmacological grouping, indicating pharmacological profile numbering (column 2), pharmacological profile (column 3), main indication(s) (column 4), name of the compound (column 4), the dose range (column 5), and the company producing or selling said compound (column 6). Compounds indicated by hatching are preferred.

20

Figure 1: Add-on treatment with pipamperon after treatment with citalopram .

Figure 2: HDRS-17 change from baseline: combo treatment pipamperon as add-on - citalopram vs SNRI (duloxetine) in Major Depression.

25

Figure 3: Remission rates (HDRS-17 <=7): combo treatment pipamperon as add-on - citalopram vs SNRI (venlafaxine) vs SSRIs vs placebo in Major Depression.

30 **Figure 4:** Fore-going treatment during 1-5 days with pipamperon followed with the combination treatment of pipamperon and citalopram.

Figure 5: HDRS-17 change from baseline: combo treatment pipamperon - citalopram with a fore-going treatment of 4 days with pipamperon vs SNRI (duloxetine) in Major Depression.

35

- Figure 6:** Remission rates (HDRS-17 <=7): combo pipamperon - citalopram with a fore-going treatment of 4 days with pipamperon vs SNRI (venlafaxine) in Major Depression.
- 5 **Figure 7:** Fore-going treatment during 6-8 days with pipamperon followed with the combination treatment of pipamperon and citalopram.
- 10 **Figure 8:** HDRS-17 change from baseline: combo treatment pipamperon - citalopram with a fore-going treatment of 7 days with pipamperon vs SNRI (duloxetine) in Major Depression.
- Figure 9:** Fore-going and add-on treatment with pipamperon in MDD.
- 15 **Figure 10:** HDRS-17 change from baseline: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SNRI duloxetine in Major Depression.
- 20 **Figure 11:** Remission rates (HDRS-17 <=7): fore-going and add-on treatment with pipamperon and citalopram in comparison with the SNRI venlafaxine in Major Depression.
- 25 **Figure 12:** Y-BOCS total score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.
- Figure 13:** Y-BOCS obsession score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.
- 30 **Figure 14:** Y-BOCS compulsion score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI fluvoxamine in OCD.
- Figure 15:** CGI-severity score: fore-going and add-on treatment with pipamperon and citalopram in comparison with the SSRI in panic disorder.

Table 1

	D1	D2	D3	SHT _{1a}	SHT _{1b}	SHT _{1c}	SHT _{6rat}	SHT _{7rat}	Alpha1	Alpha2	Beta1	Beta2	H1
ORG5222	-0.2	-0.2	-0.2	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	7.8	>9
Zotepine	0	<6	<6	6.7	7.8	7.8	6.7	0	0	0	0	6-7	<6
Flupaoxan	0	<6	<6	6.7	<6	6.7	0	0	<6	0	0	6-7	<6
Olanzapine	7.8	7.8	7.8	<6	6.7	6.7	<6	6.7	0	0	0	6-7	<6
Clozapine	7.8	6.7	6.7	6.7	6.7	6.7	6.7	6.7	7.8	7.8	7.8	7.8	>9
S16924	0	7.8	7.8	0	0	0	0	0	7.8	7.8	7.8	7.8	>9
S18327	7.8	7.8	6.7	7.8	0	0	0	0	6.7	0	0	6-7	<6
Amperozide	6.7	6.7	6.7	<6	0	0	0	0	<6	0	0	0	0
GGR218231	<6	7.8	7.8	6.7	<6	6.7	0	0	<6	0	0	6-7	<6
Serindole	7.8	7.8	7.8	6.7	7.8	7.8	6.7	6.7	0	0	0	6-7	<6
MDL100,907	6.7	<6	<6	0	0	0	0	0	7.8	0	0	<6	<6
Haloperidol	7.8	7.8	7.8	<6	6.7	<6	<6	<6	<6	0	0	0	0
Tiospritone	7.8	7.8	7.8	0	0	0	0	0	0	0	0	6-7	<6
Ractopride	<6	7.8	7.8	<6	0	0	0	0	<6	0	0	<6	<6
Fluspirilene	0	7.8	7.8	<6	<6	0	0	0	0	0	0	0	0
Ocaperidone	7.8	7.8	7.8	0	0	0	0	0	7.8	0	0	0	0
Risperidone	7.8	7.8	7.8	6.7	6.7	6.7	<6	<6	0	0	0	7.8	<6
S33084	6.7	7.8	7.8	<6	6.7	6.7	0	0	6-7	7.8	0	0	0
L741626	6.7	7.8	7.8	<6	<6	<6	0	0	6-7	<6	0	0	0
Seroquel	6.7	6.7	6.7	6.7	<6	<6	<6	<6	6-7	0	0	6-7	<6
Yohimbine	0	6.7	<6	7.8	6.7	7.8	0	0	<6	0	0	6-7	<6
Ziprasidone	0	6.7	6.7	<6	6.7	6.7	<6	<6	0	0	0	6-7	7.8
Pipamperon	0	6.7	6.7	<6	6.7	6.7	<6	<6	0	0	0	6-7	7.8

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Table 2

VISITS Day / Week / Month	ACUTE PHASE**												EXTENSION PHASE***												FOLLOW-UP PHASE						
	V1 Screen minus D7	V2 Baseline D0	V3 D4	V4 D7	V5 W1	V6 W2	V7 W3	V8 W4	V9 W5	V10 W6	V11 W7	V12 W8	V13 W9	V14 W10	V15 W11	V16 W12	M1 W13	M2 W14	M3 W15	M4 W16	M5 W17	M6 W18	M7 W19	M8 W20	M9 W21	M10 W22	M11 W23	M12 W24	M13 W25	M14 W26	M15 W27
TREATMENT GROUP																															
Group Ppi-Active / D7	A	B	C																												
Group Ppi-Active / D4	A	B	C																												
Group Ppi-Active / D0	A	B	C																												
Group Pce-Active / D0	A	D																													
Informed Consent																															
NEC/CE																															
Vital Signs / Weight																															
LAB																															
ECG																															
Phys Exam																															
Alc/Drugs Screen																															
CGI-S****																															
Q-LES-Q*****																															

Treatment regimen:

A: PLC + PLC

B: 2x(PLC+PIP(4mg))/d

C: 2x(CIT(10mg)+PIP(4mg))/d

D: 2x(CIT(10mg)+PLC)/d

*Neuronal E-Clinical Trial = Vesalius Expert Development for this Trial which includes the bottom-up measurement of:

**Entering Acute Phase: only NON-placebo responders as defined by the DSM-IV criteria of efficacy

***Entering Extension Phase: only remitters as defined by the DSM-IV criteria of efficacy

****CGI-S : Clinical Global Impressions-Improvement Scale

*****Q-LES-Q : Quality of Life, Enjoyment and Satisfaction Questionnaire

Table 3

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*Neuronal E-Clinical Trial = Vesalius Expert Development for this Trial which includes the bottom-up measurement of: Int. and evol. sociocultural

- In- and exclusion criteria
 - Functional status evaluation
 - Medical history
 - Pre-treatment signs & symptoms
 - DSM-IV rules for diagnosis & efficacy
 - Rating Scales: HDRS-28, MADRS, HAMA
 - Medical resource utilisation
 - Pre- & Concomitant medication
 - Drug administration
 - Adverse events
 - Admission to the acute and extension phases
 - Right timing of the intervention

• Entering Acute Phase: only NON-placebo responders as defined by the DSM-IV criteria of efficacy

.....Entering Extension Phase: only remitters as defined by the DSM-IV criteria

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Table 4

5

DAY	minus D7	D0	=>D4
TREATMENTGROUP			
Placebo (PLC)	PLC+PLC	2x(PLC+PLC)	2x(PLC+PC)
PIP - Active / Day 4	PLC+PLC	2x(PLC+PIP (4mg))/d	2x(CIT (10mg)+PIP (4mg))/d
PIP - Active / Day 0	PLC+PLC	2x(CIT (10mg)+PIP (4mg))/d	2x(CIT (10mg)+PIP (4mg))/d
PLC - Active / Day 0	PLC+PLC	2x(CIT (10mg)+PLC)/d	2x(CIT (10mg)+PLC)/d

10

Table 5

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GLOSSARY	
S-HT = serotonin	
S-HT1 = serotonin 1A receptor	
S-HT1A = serotonin 1A receptor	
S-HT1B = serotonin 1B receptor	
S-HT2A/D4 = serotonin 2A, en dopamine D4 receptor	
S-HT2B = serotonin 2B receptor	
S-HT2C = serotonin 2C receptor	
S-HT3 = serotonin 3 receptor	
S-HT5 = serotonin 5 receptor	
AMPA = alpha-amino-3-hydroxy-5-methyl-4-isoxazole propionate	
CB1 = cannabinoid receptor 1	
CINODs = COX-inhibiting nitric oxide inhibitors	
COX = cyclooxygenase	
COX-2 = cyclooxygenase 2	
CRF-1 = Corticotropin-Releasing Factor Receptor 1	
D1 = Dopamine 1	
D2 = Dopamine 2	
D2 = Dopamine 3	
DA = Dopamine	
ERK = extracellular signal-related kinase	
GABA = gamma-aminobutyric acid	
GABA-A = Gamma-aminobutyric acid A receptor	
GABA-B = Gamma-aminobutyric acid B receptor	
GPCR = G-Protein-Coupled Receptor	
H3 = histamine H3-receptor	
MAO = monoamine oxidase	
MAO-A = monoamine oxidase A	
MAO-B = monoamine oxidase B	
MC4 = melanocortin-4 receptor	
MCH = Melanin-concentrating hormone	
MGUR = metabotropic glutamate receptor	
MT = melatonin receptor	
NARI = selective nor-adrenergic re-uptake inhibitor	
NASSA = noradrenergic-specific serotonin reuptake inhibitor	
NDRI = selective norepinephrine and dopamine re-uptake inhibitor	
NGF = nerve growth factor	
NIK1 = neurokinin 1 receptor	
NC2 = neurokinin 2 receptor	
NGF = neurokinin 3 receptor	
NMDA = N-Methyl-D-aspartate	
NSAID = Non-steroidal anti-inflammatory drugs	
PDE4 = phosphodiesterase-4	
RIMA = reversible inhibitor of mono-amine oxidase A	
SCI-11 = G protein-Coupled receptor	
SDA = Serotonin/Dopamine Antagonists	
SDRI = selective serotonin and dopamine reuptake inhibitor	
SNDRI = selective serotonin, nor-adrenergic and dopamine reuptake inhibitor	
SSRI = selective serotonin and norepinephrine reuptake inhibitor	
VIB = selective serotonin reuptake inhibitor	
VIB = vesicular serotonin 1B receptor	

Table 6

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Examples

Example 1: Measuring pKi values of test compounds

- In Table 1, the pKi values of test compounds are given for each of the dopamine receptors, 5HT receptors, adrenergic receptors and the histamine1 receptor. The affinity of test compounds for the respective receptors has been performed according to conventional procedures known in the art.
- An indication "0" means that no affinity has been measured between the test compound and the receptor.
- 10 The columns displaying the pKi values for the D4 and the 5-HT2A receptor are filled with dark grey. pKi values between 8 and 9 and higher than 9 are represented by light grey boxes.

Example 2: Foregoing pipamperon-citalopram treatment in major depressive disorder: a placebo and active controlled period finding clinical trial

- Table 2 represents the set-up of a clinical trial comprising four treatment groups:
- Group Plc – Active / Day 0 represents the group receiving 10 mg citalopram, twice a day, starting the first day (Day 0) of active treatment in the clinical trial. This administration regime is also indicated as the mono therapy.
- 20 Group Pip - Active / Day 0 represents the group receiving a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the first day (Day 0) of active treatment in the clinical trial. This administration regime is also indicated as the non-foregoing combo therapy.
- Group Pip - Active / Day 4 represents the group receiving 4 mg pipamperon, twice a day, starting the first day (Day 0) of active treatment in the clinical trial, followed by a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the fifth (Day 4) day of active treatment in the clinical trial. This administration regime is also indicated as the foregoing therapy with combination therapy starting after 4 days of active treatment.
- 25 Group Pip - Active / Day 7 represents the group receiving 4 mg pipamperon, twice a day, starting the first day (Day 0) of active treatment in the clinical trial, followed by a combination of 4 mg pipamperon and 10 mg citalopram, twice a day, starting the eighth (Day 7) day of active treatment in the clinical trial. This administration regime is also

indicated as the foregoing therapy with combination therapy starting after 7 days of active treatment.

All subjects also undergo a placebo (PLC) run-in therapy, administered during a period of about 7 days before the active treatment starts.

5 During daily (D), weekly (W) or monthly (M) visits, several parameters are measured.

Under NECT is to be understood: Neuronal E-clinical Trial = Vesalius Expert development for this trial which includes the bottom-up measurement of:

- In- and exclusion-criteria
- Functional status evaluation
- 10 - Medical history
- (Pre-)treatment signs & symptoms
- DSM-IV rules for diagnosis & efficacy
- HDRS-28 (Hamilton Depression Rating Scale - 28 items)
- Medical resource utilisation
- 15 - Pre-trial & Concomitant medication
- Drug administration
- (Serious) Adverse events
- Admission to the acute and extension phase of treatment
- Right flow of the trial

20

Example 3: combo pipamperon-citalopram: therapeutic use in Major Depression

25 **Purpose**

Pipamperon (1'-[3-(p-Fluorobenzoyl)propyl][1,4'-bipiperidine]-4'-carboxamide), the active ingredient of Dipiperon (Janssen-Cilag B.V), administered to patients in a dose ranging between 8 and 12 mg is claimed via its specific pharmacological properties to be a booster of the antidepressant effect of the selective serotonin re-uptake inhibitor citalopram. Preferably, pipamperon is administered daily at least 4-5 days before administering said antidepressant. The mechanism of boosting of pipamperon has to deal with (i) the selective affinity for the dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other dopamine receptors, and (ii) the selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards other 5HT receptors. This semi-naturalistic open label study investigated the efficacy and tolerability of the combo pipamperon - citalopram in the treatment of patients with major depression.

Details

Design: Semi-naturalistic i.e. inclusion of every 'natural' patient in an outpatient practice but without concomitant use of mood enhancing drugs, open label

Control: No

Phase: Phase IIa – preliminary Proof of Concept

Location: Belgium – Research Centre ANIMA, Alken

End Points : Assessment scale scores, Hamilton Depression Rating Scale 17 items, Reduction, Response, Remission

Medication: Exclusion of mood stabilisers, antipsychotics (typical and atypical) and other antidepressants

Subjects

Type	No.	Sex	Age
Patients	23	10 male & 13 female	23-80 (mean 47) years

- 5 Characteristics: patients had a major depressive disorder according to DSM-IV criteria, with or without a chronic course and a treatment refractory state towards another SSRI then citalopram.

Treatments

- 10 PIP-CIT¹ add-on: citalopram from day minus 60-20 – pipamperon from DAY 0

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon ¹	+ Pip.: 8-12 mg/day – Cit.: 20-	PO	bid	8 weeks
Citalopram ¹	40 mg/day			

1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

15

- PIP-CIT¹ fore-going 1-5: pipamperon from day 0 – cital from day 1-5

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon ¹	+ Pip.: 8-12 mg/day – Cit.: 20-	PO	bid	8 weeks
Citalopram ¹	40 mg/day			

- 20 1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

PIP-CIT¹ fore-going 6-8: pipamperon from day 0 – citalopram from day 6-8

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperon ¹	+ Pip.: 8-12 mg/day – Cit.: 20-	PO	bid	8 weeks
Citalopram ¹	40 mg/day			

- 5 1. Pipamperon (Pip) and citalopram (Cit) dosage was adjusted according to clinical response.

Results

	<u>PIP-CIT add-on</u>	<u>PIP-CIT foregoing</u>	
	After 20-60 DAYS (mean 33) (n = 5)	1-5 DAYS (mean 4) (n = 15)	6-8 DAYS (mean 7) (n = 3)
Mean Used Medication			
Pipamperone	9mg/day	10mg/day	11mg/day
Citalopram	30mg/day	26mg/day	30mg/day
Depression scale scores			
HDRS 17-item total score			
baseline	29	23	28
endpoint (week 8)	4	5	11
diminishment at week 8	-25 (+8/-9)	-18 (+8/-8)	-17 (+17/-17)
% reduction at week 8	86 (+14/-12)	80 (+20/-30)	61 (+39/-61)
response ¹ at week 8	5 (100%)	15 (100%)	2 (67%)
remission ² at week 8	4 (80%)	10 (67%)	1 (33%)

- 10 1. Response = ≥50% reduction in HDRS 17-item score;
2. Remission = HDRS 17-item score < 8

Notably, the results obtained are highly significant since the variability in every group is distributed evenly around the mean.

15

Add-on PIP-CIT

Figure 1 schematically depicts the "add-on" treatment with pipamperon 8-12 (mean 9) mg (bid) after treatment with citalopram 10-20 (mean 30) mg (bid) during 20-60 (mean 33)

days (PIPCIT ADD-ON) with HDRS-17. Totalscore is 29 at baseline in MDD in comparison with the standard efficacy of antidepressants in clinical trials according to Khan et al. (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 5 2000).

Figure 2 schematically depicts the HDRS-17 change from baseline in the combo pipamperon as "add-on" to citalopram vs SNRI (duloxetine) in Major Depression. Treatment with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after 10 treatment with SSRI (n=5). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein et al., (Clin. Psychiatry, in press).

Figure 3 schematically depicts the remission rates (HDRS-17 <=7) with the combo pipamperon as "add-on" to citalopram vs SNRI (venlafaxine) vs SSRIs vs placebo in 15 Major Depression. Treatment with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n=5). Treatment with the SNRI venlafaxine is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241).Treatment with SSRIs is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with placebo is according to a meta-analysis of Thase et al. (Br. J. 20 Psychiatry (2001) 178:234-241).

Fore-going 1-5 PIP-CIT

Figure 4 schematically depicts the "fore-going" treatment during 1-5 (mean 4) days with pipamperon 8-12 (mean 10) mg (bid), followed with the combination treatment of 25 pipamperon and citalopram 20-50 (mean 26) mg/day (bid) (PIPCIT FG 1-5) in MDD (HDRS-17 at BL = 23) in comparison with the standard efficacy of antidepressants in clinical trials according to Khan et al. (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

30 Figure 5 schematically depicts the HDRS-17 change from baseline in the combo pipamperon-citalopram treatment with a "fore-going" treatment of 4 days with pipamperon (10 mg/day) vs SNRI (duloxetine) in Major Depression. Treatment with the combo pipamperon-citalopram with pipamperon 8-12 (mean 10 mg/day) (bid) 1-5 (mean 4) days 35 before treatment with SSRI (n=15). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein et al., (Clin. Psychiatry, in press).

Figure 6 schematically depicts the remission rates (HDRS-17 <=7) with the combo pipamperon with a "fore-going" treatment of 4 days with pipamperon (10 mg/day) vs SNRI (venlafaxine) in Major Depression. Treatment with the combo pipamperon-citalopram was
5 with pipamperon 8-12 (mean 10 mg/day) during 1-5 (mean 4) days before treatment with the SSRI (n=5). Treatment with the SNRI venlafaxine is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241).Treatment with SSRIs is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-241). Treatment with placebo is according to a meta-analysis of Thase et al. (Br. J. Psychiatry (2001) 178:234-
10 241).

Fore-going 6-8 PIP-CIT

Figure 7 schematically depicts the "fore-going" treatment during 6-8 (mean 7) days with pipamperon 8-12 (mean 11) mg/day (bid), followed with the combination treatment of
15 pipamperon and citalopram 20-40 (mean 30) mg/day (bid) (PIPCIT FG 6-8) in MDD (HDRS-17 at BL = 28) in comparison with the standard efficacy of antidepressants in clinical trials according to Khan et al. (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

20 Figure 8 schematically depicts the HDRS-17 change from baseline in the combo pipamperon-citalopram treatment with a "fore-going" treatment of 7 days with pipamperon (11 mg/day) vs SNRI (duloxetine) in Major Depression. Treatment with the combo pipamperon-citalopram with pipamperon 8-12 (mean 11 mg/day) (bid) 6-8 (mean 7) days
25 before treatment with SSRI (n=3). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein et al., (Clin. Psychiatry, in press).

Comparison "add-on" vs "fore-going"

Figure 9 schematically depicts a comparison between "fore-going" and "add-on"
30 treatments with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in MDD in comparison with the standard efficacy of antidepressants in clinical trials according to Khan et al. (2000), in "Symptom Reduction and Suicide Risk in Patients Treated With Placebo in Antidepressant Clinical Trials" (Arch. of General Psychiatry, Vol. 57, April 2000).

Figure 10 schematically depicts a comparison between "fore-going" and "add-on" treatments. In particular, the HDRS-17 change from baseline between "fore-going" and "add-on" treatment with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SNRI duloxetine in Major Depression is depicted. Treatment
5 with the combo pipamperon as "add-on" to citalopram, with pipamperon 8-12 mg/day (mean 9 mg/day) 20-60 (mean 33) days after treatment with the SSRI (n=5). Treatment with the combo pipamperon-citalopram, with pipamperon 8-12 mg/day (mean 11 mg/day; bid) 6-8 days (mean 7 days) before treatment with the SSRI (n = 15). Treatment with the
10 combo pipamperon-citalopram, with pipamperon 8-12 mg/day (mean 10 mg/day; bid) 1-5 days (mean 4 days) before treatment with the SSRI (n = 15). The SNRI (duloxetine) treatment was 40-120 mg/day (n = 152) according to Goldstein et al., (Clin. Psychiatry, in
press).

Figure 11 schematically depicts the remission rates (HDRS-17 <=7) in a comparison
15 between "fore-going" and "add-on" treatment with pipamperon (8-12 mg/day; bid) and citalopram (20-40 mg/day; bid) in comparison with the SNRI venlafaxine in Major Depression. Treatment with the combo pipamperon-citalopram was with pipamperon 8-12 (mean 10 mg/day) during 1-5 (mean 4) days before treatment with the SSRI (n = 15). Treatment with the SNRI venlafaxine is according to a meta-analysis of Thase et al. (Br. J.
20 Psychiatry (2001) 178:234-241). Treatment with pipamperon as "add-on" to citalopram, with pipamperon 8-12 (mean 9 mg/day) during 20-60 (mean 33) days after treatment with SSRI (n = 5).

The intention-to-treat / last-observation-carried-forward analysis showed a high
25 therapeutic efficacy according HDRS 17-item in all the treatment groups. This was especially true for the 'add-on' group probably caused by the longer treatment with an active antidepressant (+33 days). The huge therapeutic effect observed in the 'PIP-CIT 1-5' group present for at a mean dosage of pipamperon of 10 mg per day and administered the first four days of treatment without an active antidepressant, indicates
30 the boosting effect of pipamperon on the SSRI citalopram at an extremely and thus unconventional low dose. Only 1 patient discontinued treatment due to a lost of follow-up.

Adverse Events

Side effects (patients)	PIP-CIT add-on After 20-60 DAYS (mean 33) (n = 5)	PIP-CIT foregoing	
		1-5 DAYS (mean 4) (n = 15)	6-8 DAYS (mean 7) (n = 3)
Discontinued treatment due to adverse events	0	0	0
By system:			
body as a whole	0	0	0
central and peripheral nervous system	1(20%)	4(26.6%)	0
gastrointestinal	1(20%)	5(33%)	2(66.6%)
musculoskeletal	1(20%)	3(20%)	0
psychiatric	0	0	0
respiratory	0	1(6.6%)	0
skin and appendages	1(20%)	2(13.3%)	1(33.3%)
vascular	0	1(6.6%)	0
urinary	0	1(6.6%)	0

Laboratory parameters, ECG, bodyweight and vital signs were not measured since this was a naturalistic study.

5

AssessmentOutcome

Efficacy: the 4-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day is comparable to the add-on combo pipamperon-citalopram.

- 10 **Efficacy:** the 4-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day is larger than the 7-day fore-going combo pipamperon 8-12mg/d - citalopram 20-40mg/day.

Efficacy: the combo pipamperon 8-12mg/d - citalopram 20-40mg/day is larger than the in the art known antidepressants SSRIs.

15

Tolerability

Tolerability: the 4-day fore-going treatment is comparable to the 7-day fore-going combo is comparable to add-on combo pipamperon-citalopram.

Tolerability: no discontinued treatment due to adverse events.

5

Study Messages

The boosting effect of pipamperon at an extremely unconventional low dose on a SSRI is indicated since the efficacy of the 'add-on' and '4-day fore-going' combo 'pipamperon 8 -12 mg/d - citalopram 20 - 40 mg/day' is in this study as twice higher as

10 known in the art in the treatment of patients with major depression.

The combo pipamperon-citalopram is generally well tolerated in patients with depression i.e. at least no specific added adverse events were occurring by adding pipamperon at the doses used in the study.

15

Example 4: combo pipamperon-citalopram: therapeutic use in Obsessive-Compulsive Disorder (OCD).

Purpose

5 Pipamperon (1'-[3-(p-Fluorobenzoyl)propyl][1,4'-bipiperidine]-4'-carboxamide), the active ingredient of Dipiperon (Janssen-Cilag B.V), administered to a patient in a dose ranging between 8 and 12 mg is claimed via its specific pharmacological properties to be a booster of the effect of the selective serotonin re-uptake inhibitor citalopram towards OCD. Preferably, pipamperon is administered daily at least 4-5 days before
 10 administering said antidepressant. The mechanism of boosting of pipamperon has to deal with (i) the selective affinity for the dopamine-4 (D4) receptor with a pKi value equal to or higher than 8 towards the D4 receptor and less than 8 towards other Dopamine receptors, and (ii) the selective affinity for the 5-HT2A receptor with a pKi value equal to or higher than 8 towards the 5-HT2A receptor and less than 8 towards
 15 other 5HT receptors. This semi-naturalistic open label study investigated the efficacy and tolerability of the combo pipamperon - citalopram in the treatment of patients with OCD.

Details

Design: Semi-naturalistic i.e. inclusion of every 'natural' patient in an outpatient practice but without concomitant use of mood enhancing drugs, open label

Control: No

Phase: Phase IIa – preliminary Proof of Concept

Location: Belgium – Research Centre ANIMA, Alken

End Points : Assessment scale scores, Yale-Brown Obsessive-Compulsive Scale, Reduction, Remission

Medication: Exclusion of mood stabilisers, antipsychotics (typical and atypical) and other antidepressants

20

Subjects

Type	No.	Sex	Age
Patients	7	1 male & 7 female	20-63 (mean 33) years

Characteristics: patients had an obsessive-compulsive disorder according to DSM-IV criteria, with or without a chronic course and a treatment refractory state towards another SSRI then citalopram.

5 **Treatments**

PIP-CIT¹ ADD-ON: citalopram from DAY minus 730-60 – pipamperon from DAY 0

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperone ¹	+ Pip.: 8-16 mg/day – Cit.: 30-80	PO	bid	12
Citalopram ¹	mg/day			weeks

1. Pipamperone (Pip) and Citalopram (Cit) dosage was adjusted according to clinical
10 response.

PIP-CIT¹ FORE-GOING 4-6: pipamperon from DAY 0 – citalopram from DAY 4-6

Drug/Treatment	Dose	Route	Frequency	Duration
Pipamperone ¹	+ Pip.: 8-16 mg/day – Cit.: 30-80	PO	bid	12
Citalopram ¹	mg/day			weeks

- 15 1. Pipamperone (Pip) and Citalopram (Cit) dosage was adjusted according to clinical
response.

Results

	PIP-CIT add-on after 730-60 DAYS (mean 241) (n = 6) with mean Cit. 54mg/d and Pip. 11mg/d
	PIP-CIT foregoing 4-6 DAYS (mean 5) (n = 2) with mean Cit. 60mg/d and Pip. 10mg/d
Y-BOCS score	
Baseline	
Total	31
Obsessions	18
Compulsions	13
Endpoint (week 12)	
Total	15
diminishment	-16 (+16/-11)
% reduction	53
Obsessions	
total	8
diminishment	-10 (+9/-7)
% reduction	57
Compulsions	
total	7
diminishment	-6 (+7/-6)
% reduction	45
% Remission	
YBOCS score ≤8	29
BOCS score ≤16	57

Notably, the results obtained are highly significant since the variability in every group is
5 distributed evenly around the mean.

Figure 12 schematically depicts the Y-BOCS total score: "fore-going" and "add-on" treatment with pipamperon (8-15 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-

citalopram ($n = 7$). Treatment with fluvoxamine (controlled release) mean 271 mg/day ($n = 253$) is according to Hollander et al. (2003).

Figure 13 schematically depicts the Y-BOCS obsession score: "fore-going" and "add-on" treatment with pipamperon (8-15 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-citalopram ($n = 7$). Treatment with fluvoxamine (controlled release) mean 271 mg/day ($n = 253$) is according to Hollander et al. (2003).

Figure 14 schematically depicts the Y-BOCS compulsion score: "fore-going" and "add-on" treatment with pipamperon (8-16 mg/day; bid) and citalopram (30-80 mg/day; bid) in comparison with the SSRI fluvoxamine in OCD. Treatment with the combo pipamperon-citalopram ($n = 7$). Treatment with fluvoxamine (controlled release) mean 271 mg/day ($n = 253$) is according to Hollander et al. (2003).

The intention-to-treat / last-observation-carried-forward analysis showed a high therapeutic efficacy according Y-BOCS total score, obsession and compulsion scores. This indicates the boosting effect of pipamperon on the SSRI citalopram at an extremely and thus unconventional low dose. No patient discontinued treatment.

Assessment
Efficacy: the combo pipamperone 8-16mg/d - citalopram 30-80mg/day > the in the art known compounds effective towards OCD (Hollander E, Koran LM, Goodman WK, Greist JH, Ninan PT, et al. A double-blind, placebo-controlled study of the efficacy and safety of controlled-release fluvoxamine in patients with obsessive-compulsive disorder. Journal of Clinical Psychiatry 64: 640-647, Jun 2003 Mount Sinai School of Medicine, New York, New York, USA; Solvay Pharmaceuticals Inc., Marietta, Georgia, USA).

Study Messages
The boosting effect of pipamperon at an extremely unconventional low dose on a SSRI is indicated since the efficacy of the 'add-on' and 'fore-going' combo 'pipamperon 8-15 mg/d - citalopram 30-80 mg/day' is in this study as twice higher as known in the art in the treatment of patients with obsessive-compulsive disorder.

Example 5: combo pipamperon-citalopram: therapeutic use in Panic Disorder.**Purpose**

Preliminary examination of a "fore-going" and "add-on" treatment with pipamperon and
5 citalopram in comparison with the SSRI in Panic Disorder.

Results

The results are indicated in Figure 15. Figure 15 schematically depicts the CGI-severity
score: "fore-going" and "add-on" treatment with pipamperon (8 mg/day; bid) and
10 citalopram (20-40 mg/day; bid) in comparison with the SSRI in Panic Disorder. Treatment
with the combo pipamperon-citalopram (n = 3). Treatment with paroxetine is according to
the Journal of Clinical Psychiatry (2004) 65: 405-413. Treatment with Sertraline is
according to the Journal of Clinical Psychiatry (2004) 65: 405-413.

15 Conclusion

Notably, although a small test group has been used (n = 3), the distribution around the
mean is good. It will further be apparent from Figure 15 that the effect of the combo
treatment of pipamperon and citalopram is twice as high as the standard treatments with
paroxetine or sertraline.

20

Example 6: POC process for mayor depressive disorder

Concept: Combo of the high selective 5-HT2A/D4 antagonist pipamperon with:

- 25 - a compound active towards the Amino Acid Transmitter, Peptidergic Transmitter,
Adenosine Transmitter, Endocrine and/or Enzymatic System;
- a fore-going admission during 4 days of pipamperon;
- a dose of pipamperon of 12 mg/day

30 Objectives: Demonstrating that this combo therapy has:

- the potency of being a treatment standard for depression by having an added value of
reducing the total score of the Hamilton Depression Rating Scale – 17 items (HDRS-
17) after 8 weeks of therapy with a least 20% more than reached with the conventional
known antidepressants, i.e. 60% versus 40%. This stands for an added medium
35 demission of 5 points on the total score of the HDRS-17 and by this will be very highly

significant since the mean difference in all recent clinical trials between placebo and active treatment is 2.5;

- a more sustained therapeutic effect than the conventional mono therapy by preventing significant more relapses during 48 weeks following the acute treatment; and/or
- 5 - a complete neutral safety profile, e.g. there are no more adverse events in the combo therapy then in mono admission of the in the combo used antidepressant compound.

Process: the following different steps were implemented to reach out for these objectives (see also Tables 3 and 4):

10 (1) an naturalistic open label study ($n \geq 20$) on a depressive population with a normal variability of medical and psychiatric history, course of depression, earlier and concomitant therapy admitting the golden standard antidepressant citalopram 20-40 mg/day and a dose of 8-12 mg/day of pipamperon in a foregoing, simultaneous or add-on use.

15 (2) a 16 weeks placebo controlled randomised four armed study of each 36 patients with a mayor depressive disorder admitting:

- from day 0: placebo or pipamperon (PIP) 10 mg/day or an active antidepressant compound or the combination of the last two;
- from day 4: placebo or pipamperon 10 mg/day combined with an active antidepressant compound or an active antidepressant compound without pipamperon.

20 By including rigorous control groups (placebo and active comparator; see Tables 3 and 4) this clinical trial is evaluated as a proof of concept of the added value of the combo and the foregoing treatment method since the inclusion/exclusion of:

- 25 - a negative trial, i.e. no significant difference between the placebo and active treatment with the comparator;
- a failed trial, i.e. no significant difference between the active and the studied treatment i.e. the combo.

(3) an active controlled randomised relapse prevention study following the POC trial 30 during another 36 weeks with three arms of each 36 patients which is formed by:

- continuation of the active mono therapy;
- randomising the patients with a combo therapy in a group with an active mono therapy and with a continuation of the combo treatment.

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